

“Develop your own passion. Work on it hard. It is not easy; but if you find it, you will be the happiest person on earth. I guarantee you will jump from bed at 6 o’clock to go to work.

...

Be compassionate; when you are on the way up or at the top, don’t forget those who are struggling at the bottom”.

**Prof. Ahmed Zewail
(1946-2016)**

Preface

In the past, physicians relied solely on their own judgment, experience, and the knowledge gained from medical school to make treatment decisions for patients. However, we now understand that this is not the best way to practise medicine because what physicians think is best for a patient is not always what the research shows is best.

When researchers study a disease or a condition, they usually look at many more patients than any one physician will ever treat. Also, medical knowledge changes all the time. So, only by looking at all the evidence and judging it fairly, you can work out what the research really says about a treatment. This is called practising evidence-based medicine (EBM). This concept has revolutionized clinical practice worldwide and continues to change the medical world, providing healthcare professionals a tool to determine which treatments work and which do not. Thus, it is not surprising that, in 2007, when The BMJ chose the top 15 milestones in medicine over the last 160 years, EBM was one of them, next to achievements as anesthesia, antibiotics, the discovery of DNA structure, and vaccines.

For instance, the perception of beta blockers as being absolutely contraindicated in patients with congestive heart failure (CHF) underwent a conceptual revolution after a number of large randomized clinical trials have been conducted and most of beta blockers have shown benefit in such patients. Since then, they have become a cornerstone in the treatment of symptomatic CHF.

This book is a practical tool designed to support everyday clinical practice, drawing on current practice guidelines from esteemed professional societies, particularly the European Society of Cardiology (ESC). In this edition, I intend to present a resource that is both updated and comprehensive while remaining concise, effectively illustrating the guidelines.

To my colleagues, I hope this book will aid you in your noble mission to save lives, alleviate suffering, and excel in your professional examinations. I extend my gratitude to all those who have provided valuable comments and insights after the first edition. I welcome your feedback and suggestions, which can be shared via email at: tothepointcardio@gmail.com or through our Facebook page: <https://www.facebook.com/To-The-Point-104817652086986/>. Your suggestions will find their way into the future editions.

Amr Yosry Emam

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Overview over the terminology used in guidelines

The Class designation is used to indicate whether a therapy is recommended or not and the certainty surrounding that recommendation.

Classes of Recommendation:

- **Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. Wording to use: Is recommended or is indicated.
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
 - **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy. Wording to use: Should be considered.
 - **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion. Wording to use: May be considered.
- **Class III:** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. Wording to use: Is not recommended.

Level of Evidence:

- **Level of Evidence A:** include data derived from multiple randomized clinical trials or meta-analyses of such studies.
- **Level of Evidence B:** include data derived from one or more randomized trials or meta-analysis of such studies and data derived from one or more non-randomized trials or meta-analysis of such studies.
- **Level of Evidence C:** include non-randomized observational studies with limitations in design or execution or Metanalysis of such studies and consensus opinion of experts based on clinical experience.

List of abbreviations

| | |
|----------|---|
| 3D | Three-dimensional |
| AAD | Antiarrhythmic drug |
| AAA | Abdominal aortic aneurysm |
| ABI | Ankle–brachial index |
| ACC | American College of Cardiology |
| ACCP | American College of Chest Physicians |
| ACE-I | Angiotensin converting enzyme inhibitor |
| ACS | Acute coronary syndrome |
| ACT | Activated clotting time |
| ADHF | Acutely decompensated heart failure |
| ADP | Adenosine diphosphate |
| AF | Atrial fibrillation |
| AFL | Atrial flutter |
| AHA | American Heart Association |
| AI | Aortic insufficiency |
| AIVR | Accelerated idioventricular rhythm |
| ANA | Antinuclear antibodies |
| Ao | Aorta |
| AoV | Aortic valve |
| AP | Accessory pathway - Anteroposterior view |
| ARB | Angiotensin-II receptor blocker |
| ARDS | Acute respiratory distress syndrome |
| ARVC | Arrhythmogenic right ventricular cardiomyopathy |
| ARVD | Arrhythmogenic right ventricular dysplasia |
| AS | Aortic stenosis |
| ASD | Atrial septal defect |
| AT | Atrial tachycardia |
| AT III | Antithrombin III |
| AV block | Atrioventricular block |
| AVA | Aortic valve area |
| AVNRT | Atrioventricular nodal reentrant tachycardia |
| AVR | Aortic valve replacement |
| AVRT | Atrioventricular reciprocating tachycardia |
| BBB | Bundle branch block |
| BiPAP | Bilevel positive airway pressure |
| BiV | Biventricular |
| biVAD | Biventricular assist device |
| BMS | Bare-metal stent |
| BNP | Brain natriuretic peptide |
| BP | Blood pressure |
| bpm | Beats per minutes |
| BSA | Body surface area |
| BUN | Blood urea nitrogen |
| Ca | Calcium |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CBC | Complete blood count |
| CCB | Calcium channel blockers |
| CEA | Carotid endarterectomy |
| CIA | Common iliac artery |
| CK | Creatine kinase |
| CK-MB | Creatine kinase MB |
| CKD | Chronic kidney disease |

| | |
|------------------|--|
| CHF | Congestive heart failure |
| CO | Cardiac output |
| COPD | Chronic obstructive pulmonary disease |
| CPAP | Continuous positive airway pressure |
| CRP | C-reactive protein test |
| CRT | Cardiac resynchronization therapy |
| CAS | Carotid artery stenting |
| CT | Computed tomography |
| CTA | Computed tomography angiography |
| CTI | Cavotricuspid isthmus |
| CTO | Chronic total occlusion |
| CTPH | Chronic thromboembolic pulmonary hypertension |
| CVP | Central venous pressure |
| CW | Continuous wave Doppler |
| CYP 450 | Cytochrome P450 |
| CXR | Chest X-ray |
| DAD | Delayed afterdepolarization |
| DBP | Diastolic blood pressure |
| DC | Direct-current cardioversion |
| DCM | Dilated cardiomyopathy |
| DES | Drug-eluting stent |
| DHP | Dihydropyridine (calcium channel blocker) |
| dP/dt | Delta pressure/delta time (sharpness of rise in pressure over time) |
| DTI | Direct thrombin inhibitor |
| DTS | Duke treadmill score |
| DVT | Deep vein thrombosis |
| EAD | Early afterdepolarization |
| ECG | Electrocardiogram |
| echo | Echocardiogram |
| ECMO | Extracorporeal membrane oxygenation |
| ED | Emergency department |
| EF | Ejection fraction |
| EP | Electrophysiological |
| ERO | Effective regurgitant orifice |
| ESC | European Society of Cardiology |
| ESR | Erythrocyte sedimentation rate |
| ESRD | End-stage renal disease |
| FFR | Fractional flow reserve |
| FiO ₂ | Fraction of inspired oxygen |
| FMD | Fibromuscular dysplasia |
| GAS | Group A beta-hemolytic streptococci |
| GFR | Glomerular filtration rate |
| GI | Gastrointestinal |
| GPI | Glycoprotein IIb–IIIa inhibitor |
| Hb | Hemoglobin |
| HbA1c | Glycosylated haemoglobin |
| HCM | Hypertrophic cardiomyopathy |
| HCTZ | Hydrochlorothiazide |
| HDL | High-density lipoprotein |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrfEF | Heart failure with reduced ejection fraction |
| HIT | Heparin-induced thrombocytopenia |
| HIV | Human immunodeficiency virus |
| HOCM | Hypertrophic obstructive cardiomyopathy |
| HR | Heart rate |

| | |
|------------|--|
| hs-CRP | High sensitivity C-reactive protein test |
| HTN | Hypertension |
| IABP | Intra-aortic balloon pump |
| ICD | Implantable cardioverter defibrillator |
| ICU | Intensive care unit |
| INR | International normalized ratio |
| IV | Intravenous or intravenously |
| IVC | Inferior vena cava |
| IVCT | Isovolumic contraction time |
| IVR | Isovolumic relaxation |
| IVRT | Isovolumic relaxation time |
| IVUS | Intravascular ultrasound |
| JVD | Jugular venous distension |
| JVP | Jugular venous pressure |
| K | Potassium |
| LA | Left atrium |
| LAA | Left atrial appendage |
| LAFB | Left anterior fascicular block |
| LAD | Left anterior descending artery |
| LAO | Left anterior oblique |
| LBBB | Left bundle branch block |
| LCx | Left circumflex coronary artery |
| LDL | Low-density lipoprotein |
| LIMA | Left internal mammary artery |
| LM | Left main |
| LMWH | Low-molecular-weight heparin |
| LPFB | Left posterior fascicular blockL |
| LV | Left ventricle or Left ventricular |
| LVAD | Left ventricular assist device |
| LVEDD | Left ventricular end-diastolic diameter |
| LVEDP | Left ventricular end-diastolic pressure |
| LVEF | Left ventricular ejection fraction |
| LVESD | Left ventricular end-systolic diameter |
| LVH | Left ventricular hypertrophy |
| LVOT | Left ventricular outflow tract |
| MAP | Mean arterial pressure |
| MAT | Multifocal atrial tachycardia |
| MET | Metabolic equivalent of task |
| mph | Miles per hour |
| MI | Myocardial infarction |
| MR | Mitral regurgitation |
| MRA | Magnetic resonance angiography |
| MRI | Magnetic resonance imaging |
| MS | Mitral stenosis |
| MV | Mitral valve |
| MVA | Mitral valve area |
| MVP | Mitral valve prolapse |
| MVR | Mitral valve replacement |
| Na | Sodium |
| NO | Nitric oxide |
| NSAID | Non-steroidal anti-inflammatory drug |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| NSVT | Non-sustained ventricular tachycardia |
| NT pro-BNP | Amino-terminal pro-brain natriuretic peptide |
| NTG | Nitroglycerin |
| NYHA | New York Heart Association |

| | |
|-------------------|--|
| OCT | Optical coherence tomography |
| OM | Obtuse marginal branch of the left circumflex |
| PA | Pulmonary arterial or Pulmonary artery |
| PAC | Premature Atrial Complex |
| PaCO ₂ | Partial pressure of carbon dioxide in arterial blood |
| PAD | Peripheral arterial disease |
| PAH | Pulmonary arterial hypertension |
| PAI | Plasminogen activator inhibitor |
| PaO ₂ | Arterial oxygen pressure |
| PCI | Percutaneous coronary intervention |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PCWP | Pulmonary capillary wedge pressure |
| PDA | Patent ductus arteriosus |
| PDA | Posterior descending artery |
| PDES | Phosphodiesterase |
| PE | Pulmonary embolism |
| PEA | Pulseless electrical activity |
| PET | Positron emission tomography |
| PFO | Patent foramen ovale |
| PFT | Pulmonary function testing |
| PH | Pulmonary hypertension |
| PHT | Pressure half-time |
| PISA | Proximal isovelocity surface area |
| PJRT | Permanent junctional reciprocating tachycardia |
| PM | Pacemaker |
| PMBV | Percutaneous mitral balloon valvuloplasty |
| PMT | Pacemaker-mediated tachycardia |
| PND | Paroxysmal nocturnal dyspnea |
| POTS | Postural orthostatic tachycardia syndrome |
| PPI | Proton pump inhibitor |
| PR | Pulmonic regurgitation |
| PS | Pulmonic stenosis |
| PTT | Partial thromboplastin time |
| PV loop | Pressure–volume loop |
| PVC | premature ventricular complex |
| PVR | pulmonary vascular resistance |
| PW | Pulsed wave Doppler |
| Qp | Pulmonary blood flow |
| Qs | Systemic blood flow |
| QTc | Corrected QT interval |
| RA | Right atrium |
| RAAS | Renin-angiotensin-aldosterone system |
| RAO | Right anterior oblique |
| RAS | Renal artery stenosis |
| RBBB | Right bundle branch block |
| RHC | Right heart catheterization |
| RCA | Right coronary artery |
| RIMA | Right internal mammary artery |
| rPA | Retepase |
| rpm | Revolutions per minute |
| RRT | Renal Replacement therapy |
| r-tPA | Recombinant tissue plasminogen activator |
| RV | Right ventricle/ventricular |
| RVAD | Right ventricular assist device |

| | |
|------------------------|--|
| RVEDP | Right ventricular end-diastolic pressure |
| RVH | Right ventricular hypertrophy |
| RVOT | Right ventricular outflow tract |
| SA | Sinoatrial |
| SaO₂ | Systemic arterial oxygen saturation |
| SAM | Systolic anterior motion |
| SBE | Subacute bacterial endocarditis |
| SBP | Systolic blood pressure |
| SCD | Sudden cardiac death |
| SIRS | Systemic inflammatory response syndrome |
| SFA | Superficial femoral artery |
| SNRT | Sinus node reentrant tachycardia |
| SPECT | Single photon emission computed tomography (nuclear imaging) |
| SQ | Subcutaneously |
| STEMI | ST-segment elevation myocardial infarction |
| STS | Society of Thoracic Surgeons |
| SV | Stroke volume |
| SVC | Superior vena cava |
| SVG | Saphenous venous graft |
| SvO₂ | Mixed venous oxygen saturation |
| SVR | Systemic vascular resistance |
| SVT | Supraventricular tachycardia |
| TAA | Thoracic aortic aneurysm |
| TdP | Torsades de pointes |
| TEE | Transesophageal echocardiogram |
| TGA | Transposition of great arteries |
| TIA | Transient ischemic attack |
| TR | Tricuspid regurgitation |
| TSH | Thyroid stimulating hormone |
| TTE | Transthoracic echocardiogram |
| UA | Unstable angina |
| UFH | Unfractionated heparin |
| VAD | Ventricular assist device |
| V/Q scan | Lung ventilation/perfusion scan |
| VF | Ventricular fibrillation |
| VLDL | Very-low-density lipoprotein |
| VSD | Ventricular septal defect |
| VSR | Ventricular septal rupture |
| VT | Ventricular tachycardia |
| VTI | Velocity-time integral |
| WPW | Wolff–Parkinson–White |

Section

1

Heart Failure and Specific Cardiomyopathies

TO THE POINT

Chapter 1

Chronic Heart Failure

Universal Definition of HF:

HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.

Classification:

- **According to Ejection Fraction:**

Traditionally, HF has been divided based on the measurement of left ventricular ejection fraction (LVEF) into: heart failure with reduced (HFrEF), mildly reduced (HFmrEF) and preserved (HFpEF) ejection fraction ⁽¹⁾. The rationale behind this relates to the original treatment trials in HF that demonstrated substantially improved outcomes in patients with LVEF ≤ 40%.

| Table 1-1: Classification of Heart Failure: | | | |
|---|---------------------------------|-------------|------------|
| | HFrEF | HFmrEF | HFpEF |
| CRITERIA | Symptoms ± Signs ⁽²⁾ | | |
| | LVEF ≤ 40% | LVEF 41-49% | LVEF ≥ 50% |

(1) There is a new class according to the universal classification of HF: **HF with improved ejection fraction (HFimpEF)** which is defined as symptomatic HF with a baseline LVEF ≤ 40%, ≥ 10-point increase from baseline LVEF, and second measurement of LVEF > 40%.

(2) Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

| | | | |
|--|--|--|---|
| | | | Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ⁽¹⁾ |
|--|--|--|---|

A patient who has never exhibited the typical symptoms and/or signs of HF and with a reduced LVEF is described as having ***asymptomatic LV systolic dysfunction***.

▪ **According to symptom progression:**

• **Universal classification of HF:**

- **Stage A (At risk for HF):** Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease.
- **Stage B (Pre-HF):** Patients without current or prior symptoms or signs of HF with one of the following:
 - Structural Heart Disease: for example, LVH, cardiac chamber enlargement, ventricular wall motion abnormality, valvular heart disease, myocardial tissue abnormality (eg, evidence of myocardial edema, scar/fibrosis abnormality by T2-weighted CMR imaging or LGE imaging).
 - Abnormal cardiac function: for example, reduced LV or RV systolic function, evidence of increased filling pressures (by invasive or noninvasive measures), abnormal diastolic dysfunction.
 - Elevated natriuretic peptide levels or elevated cardiac troponin levels (> 99th percentile in a normal reference population), especially in the setting of exposure to cardiotoxins.
- **Stage C (Heart Failure):** Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality.
- **Stage D (Advanced HF):** Severe symptoms and/or signs of HF at rest refractory or intolerant to GDMT, requiring advanced therapies such as transplantation, mechanical circulatory support, or palliative care.

(1) For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF. These abnormalities include: Elevated natriuretic peptides, relevant structural heart disease (LVH and/or LAE) and Diastolic dysfunction.

- **The NYHA functional classification:**

- **Class I (Mild):** Patients with cardiac disease but *NO limitation of physical activity*.
- **Class II (Mild):** Patients with cardiac disease but *slight limitation of physical activity*.
- **Class III (Moderate):** Patients with cardiac disease but *marked limitation of physical activity*.
- **Class IV (Severe):** Patients with cardiac disease resulting in the inability to carry on any *physical activity without discomfort*.

Epidemiology:

- The prevalence of HF depends on the definition applied but is approximately 1-2% of the adult population in developed countries, rising to $\geq 10\%$ among people > 70 years.
- The incidence of HF in Europe is $\approx 3/1000$ person-years (all age-groups) or $5/1000$ person-years in adults.
- The ESC Long-Term Registry, in the outpatient setting, reports that 60% have HFrEF, 24% have HFmrEF, and 16% have HFpEF.
- The lifetime risk of HF at age 55 years is 33% for men and 28% for women.

Pathophysiology of HFrEF:

Heart failure may be viewed as a progressive disorder that is initiated after an index event either: **(i)** damages the heart muscle, with a resultant loss of functioning cardiac myocytes (as in MI) **or**, **(ii)** disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally, (as in pressure or volume overload), **or (iii)** it may be hereditary.

The focus, here, will be on the molecular and cellular changes that underlie heart failure with reduced ejection fraction, with an emphasis on the role of LV remodeling and neurohormonal activation.

- **Left Ventricular Remodelling:**

- Alteration in myocyte structure.
- Alteration in myocyte biology.
- Alteration in LV geometry.

- **Neurohormonal Mechanisms:**

- Activation of sympathetic nervous system
- Activation of RAAS system

- **LV Remodelling:** progressive changes in shape and size of the heart due to exercise or pregnancy (physiological remodeling) or after injury to the heart muscle (pathological remodeling). Pathological remodeling may be due to gene mutations, acute myocardial injury, and abnormal loading status.

In the acute phase of a myocardial stress, cardiac remodeling acts as an adaptive response that enables the heart to maintain cardiac output; however, after the prolonged stressful stimulus, this continuous process leads to progressive decompensation.

1. **Alteration in myocyte structure:** The changes that occur in failing myocardium may be categorized broadly into those that occur in the volume of cardiac myocytes and those that occur in the volume and composition of the extracellular matrix.

- **Myocyte necrosis:** e.g: In MI: Myocardial injury → loss of membrane integrity (cell swelling) → ↓ glycogen granules → cell rupture → release of proteolytic enzymes.
- **Myocyte Apoptosis** (programmed cell death): ↑ Pro-apoptotic (Ang. II, Catecholamine, O₂, cytokines) → activation of death receptors in mitochondria and cell membrane → activation of cell capsase-g → proteolytic enzymes.
- **Extracellular matrix degradation:** During cardiac remodeling, significant increase in Matrix metalloproteinases (MMP) occurs → collagen degradation, as well as loss of collagen struts that connect the individual cardiac myocytes.

2. **Alteration in myocyte biology:**

- **Excitation-contraction coupling:** excitation-contraction coupling refers to the cascade of biologic events that begins with the cardiac action potential and ends with myocyte contraction and relaxation. Impaired contraction and relaxation of the failing heart is most prominent at high heart rates, which results in a depressed force-frequency relationship.

- **Beta-adrenergic desensitization:** ventricles obtained from HF patients demonstrate a marked reduction in beta-adrenergic receptor density. The downregulation of beta-adrenergic receptors is likely mediated by increased levels of norepinephrine. In patients with DCM, this reduction in receptor density involves primarily the beta1-receptor protein and mRNA and is proportional to the severity of HF.

Desensitization of the beta receptors can be both beneficial and deleterious in HF. By reducing LV contractility, desensitization may be deleterious. However, by reducing energy expenditure of the energy-starved myocardium and protecting the myocyte from the deleterious effects of sustained adrenergic stimulation, this adaptive response is beneficial.

- **Energy metabolism and oxidative stress:** remodeling is associated with altered energy metabolism and subsequent energy deficit with increased glucose oxidation and decreased free fatty acid oxidation. These findings lead to even lower energy availability for myocardial proteins with ATPase activity, and the excessive generation of oxygen species with associated decreased antioxidant defense. Oxidative stress occurs, leading to activation of hypertrophy signaling pathways, proliferation of fibroblasts, activation of metalloproteinases, induction in apoptosis.

- **Cardiac Myocyte Hypertrophy:**

In pressure overload hypertrophy (e.g., with AS or hypertension), increased systolic wall stress leads to the addition of sarcomeres **in parallel**, an increase in myocyte cross-sectional area, and increased LV wall thickening. This pattern of remodeling has been referred to as “**concentric**” hypertrophy and has been linked with alterations in Ca^{2+} /calmodulin-dependent protein kinase II–dependent signaling.

By contrast, in volume overload hypertrophy (e.g., with AR and MR), increased diastolic wall stress leads to an increase in myocyte length with the addition of sarcomeres **in series**, thereby increased LV ventricular dilation. This pattern of remodeling has been referred to as “**eccentric**” hypertrophy.

3. Alteration in LV geometry:

- **Increased LV sphericity:** One of the first observations regarding the abnormal geometry of remodeled ventricle was that the remodeled heart was not only larger but also more spherical in shape which results in an increase in LV wall stress, thereby creating a de novo energetic burden for the failing heart.

- **LV wall thinning:** LV wall thinning also occurs as the ventricle begins to dilate and remodel. The increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional “afterload mismatch” that may further contribute to a decrease in forward cardiac output.
- **Mitral valve incompetence:** LV dilation is that the papillary muscles are pulled apart, resulting in incompetence of the mitral valve and development of “functional mitral regurgitation.” In addition to the loss of forward blood flow, mitral regurgitation results in further volume overloading of the ventricle.

Together, the mechanical burdens engendered by LV remodeling might lead to increased LV dilation, decreased forward cardiac output, and increased hemodynamic overloading, any of which is sufficient to contribute to worsening LV function independent of the patient's neurohormonal status.

- **Neurohormonal Mechanisms:** The portfolio of compensatory mechanisms includes activation of the sympathetic nervous system and the RAAS, which are responsible for maintaining cardiac output through increased retention of salt and water; peripheral arterial vasoconstriction and increased contractility; and inflammatory mediators that are responsible for cardiac repair and remodeling.

1. Activation of sympathetic nervous system:

One of the most important compensatory adaptations is activation of the sympathetic nervous system (SNS), which occurs early in the course of HF. In patients with HF, inhibitory input from baroreceptors and mechanoreceptors decreases and excitatory input increases, with the net result of a generalized increase in sympathetic nerve traffic and blunted parasympathetic nerve traffic, leading to loss of heart rate variability and increased peripheral vascular resistance.

As a result of the increase in sympathetic tone, there is an increase in circulating levels of Norepinephrine ⁽¹⁾. The augmented adrenergic outflow from the CNS may trigger ventricular tachycardia or even sudden cardiac death, particularly in the presence

(1) *Plasma levels of NE predict mortality in patients with HF. However, as HF progresses there is a significant decrease in the myocardial concentration of NE. The mechanism responsible for cardiac NE depletion in severe HF may relate to an “exhaustion” phenomenon resulting from the prolonged adrenergic activation of the cardiac adrenergic nerves in HF.*

of myocardial ischemia. Thus, activation of the SNS provides short term support that has the potential to become maladaptive over the long term.

2. Activation of RAAS system:

In contrast with the SNS, the components of the RAAS are activated comparatively later in HF. The presumptive mechanisms for RAAS activation in HF include renal hypoperfusion, decreased filtered sodium reaching the macula densa in the distal tubule, and increased sympathetic stimulation of the kidney, leading to increased renin release from juxtaglomerular apparatus.

Renin cleaves angiotensinogen, which is synthesized in the liver, to form the biologically inactive angiotensin I. Angiotensin-converting enzyme (ACE) cleaves angiotensin I to form the biologically active angiotensin II.

Angiotensin II has several important actions that are critical to maintaining short-term circulatory homeostasis. However, the sustained expression of angiotensin II is maladaptive leading to fibrosis of the heart, kidneys, and other organs. Angiotensin II can also lead to worsening neurohormonal activation by enhancing the release of NE from sympathetic nerve endings, as well as stimulating the zona glomerulosa of the adrenal cortex to produce aldosterone.

- **Neurohormonal Alterations of Renal Function:**

One of the signatures of advancing HF is increased salt and water retention by the kidneys. Traditional theories have ascribed this to either: “forward” failure, which attributes sodium retention to inadequate renal perfusion as a consequence of impaired cardiac output, or “backward” failure, which emphasizes the importance of increased venous pressure causing transudation of salt and water from the intravascular to the extracellular compartment. These mechanisms have largely been supplanted by the concept of ***decreased effective arterial blood volume***, which postulates that inadequate cardiac output sensed by baroreceptors in the vascular tree leads to a series of compensatory neurohormonal adaptations that resemble the homeostatic response to acute blood loss.

Renal sympathetic stimulation can lead to the non-osmotic release of vasopressin from the posterior pituitary, which reduces the excretion of free water and worsens the peripheral vasoconstriction.

- **Neurohormonal Alterations in the Peripheral Vasculature:**

In patients with heart failure, the complex interactions between the autonomic nervous system and local autoregulatory mechanisms tend to preserve circulation to the brain and heart while decreasing blood flow to the skin, skeletal muscles, splanchnic organs, and kidneys. The most powerful stimulus for peripheral vasoconstriction is sympathetic activation, which releases the potent vasoconstrictor NE.

The arteriolar vasoconstriction maintains the arterial pressure, when the increased venous tone helps to maintain venous return and ventricular filling and to support cardiac performance by Starling's law.

Aetiology:

Identification of the aetiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF as the specific pathology can determine subsequent treatment. Most commonly, HF is due to myocardial dysfunction: either systolic, diastolic, or both. However, pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause or contribute to HF.

▪ **HF with reduced EF (Systolic HF):**

1. CAD: coronary artery disease (CAD) is the most common cause of HFrEF. HFrEF that is secondary to CAD is called “*Ischemic Cardiomyopathy*”. Two ischemic processes may explain LV dysfunction:

- Large transmural Q-wave MI.
- Hibernating myocardium. Severe coronary artery stenosis may cause the myocardium to “shut down,” i.e., hibernate without dying. Hibernation can be reversed with revascularization.

2. Hypertension: Hypertension is the second most common cause of systolic HF. Chronic, severe hypertension leads to diastolic dysfunction initially, followed by systolic dysfunction.

Without underlying myocardial disease or a chronic hypertensive cardiomyopathy, acute blood pressure rise does not usually cause acute LV systolic dysfunction, as a normal LV can tolerate acute pressure overload. This acute blood pressure rise more readily causes pulmonary edema through acute diastolic dysfunction.

3. Advanced valvular heart disease (MR, AR, AS)

4. Dilated cardiomyopathy (DCM)

▪ **HF with preserved EF (Diastolic HF):**

1. Hypertension (\pm LVH):

Hypertension is the most common risk factor for diastolic HF. Diastolic dysfunction may precede LV hypertrophy and is more prevalent than LV hypertrophy.

Arterial, ventricular, and atrial stiffness are increased as a result of increasing collagen, cytoskeletal proteins, and abnormal calcium homeostasis. This stiffness makes the LV filling pressure, LA pressure, and systolic blood pressure markedly increase with relatively minor volume overload.

The arterial stiffness explains a very striking rise in SBP with exercise, which is an important component of diastolic HF in many patients.

2. CAD (ischemia without infarction):

Relaxation being an active process, CAD may contribute to diastolic dysfunction.

In fact, in patients with CAD, a rise in LVEDP (diastolic stiffening) is an early hemodynamic manifestation of angina induced by exercise or pacing.

3. Hypertrophic cardiomyopathy.

4. Constrictive pericarditis: Constrictive pericarditis mimics the presentation of RCM and RV failure.

▪ **Right-sided HF:** Left-sided HF is the most common cause of right-sided HF. *Overall, there are three mechanisms of RV failure, including isolated RV failure:*

- **Pressure overload:** pulmonary hypertension secondary to left heart disease, lung disease, PE, or pulmonary vascular disease.
- **Volume overload:** ASD, tricuspid or pulmonic regurgitation. TR is often functional and secondary to RV failure but exaggerates its progression through the extra-volume load. In the absence of severe pulmonary hypertension, TR and especially PR are usually well tolerated for years before leading to RV failure. The adult RV is more tolerant of volume overload than pressure overload.

- **Intrinsic RV dysfunction:** ARVD or RV infarct.

Acute myocarditis, tachycardia-mediated cardiomyopathy, and idiopathic, HIV, or alcoholic cardiomyopathy usually lead to RV and LV involvement, but one may be more predominantly involved than the other.

N.B:

- ☞ In any patient presenting with right heart failure, do not overlook the possibility of pericardial processes, the great mimickers of right heart failure. Tamponade mimics acute right heart failure, while constrictive pericarditis mimics chronic right HF.
- ☞ Restrictive cardiomyopathy, a form of biventricular failure, frequently presents clinically as a predominant right heart failure.

Clinical Picture:

The diagnosis of CHF requires the presence of symptoms and/or signs of HF and objective evidence of cardiac dysfunction (e.g., history of MI, arterial hypertension, diabetes mellitus, alcohol misuse).

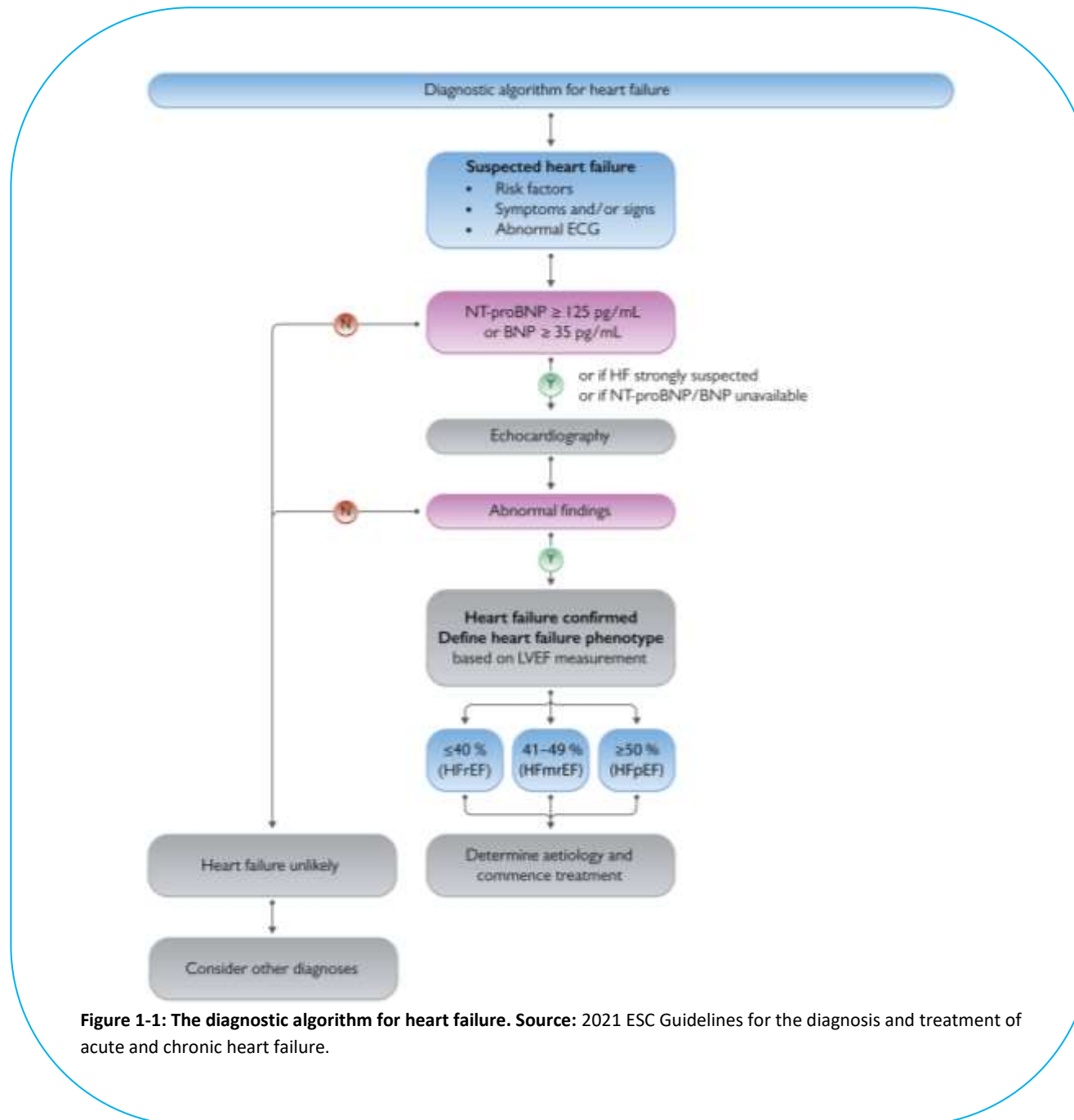


Figure 1-1: The diagnostic algorithm for heart failure. Source: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

▪ **Congestive findings** ⁽¹⁾:

- **Orthopnea and paroxysmal nocturnal dyspnea (PND)**, both relatively specific for HF. They result from the increase in venous return during recumbency and the subsequent increase in pulmonary capillary wedge pressure (PCWP). Many patients present with nocturnal cough or wheezes rather than nocturnal dyspnea; a dry cough may be a dyspnea equivalent and should suggest HF. Wheezes result from congestion of the bronchial mucosa and from the interstitial edema that narrows the small airways.

Orthopnea can be tested by asking the patient to lie supine for 2 minutes.

Beside HF, orthopnea may be seen in obese patients or those with advanced lung disease ⁽²⁾ and flattened diaphragm.

- **Exertional dyspnea**: this may be a manifestation of:

- rise in pulmonary capillary wedge pressure during exertion. The pulmonary venous engorgement stiffens the lungs and reduces vital capacity, leading to dyspnea.
- inappropriate rise in cardiac output during exertion, with a subsequent peripheral and respiratory muscle fatigue and reduced pulmonary perfusion (increased pulmonary dead space). *Thus, diuretics do not necessarily improve exertional dyspnea.*

Dyspnea is frequently described as “chest pressure” and therefore, in HF, especially decompensated HF, chest pressure is not necessarily secondary to CAD.

- **Bendopnea**: shortness of breath when leaning forward. Seen in cases of advanced HF.
- **Quick weight gain** (> 2 kg/week) or quick weight loss in response to treatment implies volume overload.
- **Increased jugular venous pulsation (JVP) ≥ 8 cmH₂O**:

(1) Congestion in heart failure is defined as signs and symptoms of extracellular fluid accumulation that result in increased cardiac filling pressures. Heart failure with increased neurohumoral activation induces a state of increased renal sodium and water avidity resulting in an increased plasma volume. Also, increased sympathetic output leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic vasculature to the circulatory volume. This increases the effective circulating volume by redistribution. As a result, venous return and cardiac filling pressures increase.

(2) **COPD-related PND** results from mucus hypersecretion and is relieved by cough and albuterol, and **Asthma-related PND** results from nocturnal bronchospasm and is relieved by albuterol.

Not only does an elevated JVP detect systemic congestion, but there is good sensitivity (70%) and specificity (79%) between high JVP and elevated left sided filling pressure.

In patients with normal JVP, a hepatojugular reflux maneuver may be performed to unveil HF: a positive result is defined as sustained rise of JVP of ≥ 4 cmH₂O following > 10 sec of pressure on the right upper quadrant during normal breathing (no Valsalva), **or** fall of JVP of 4 cmH₂O upon release of pressure.

- **S3**: in patients > 40 years, S3 is highly specific (~90%) for an elevated PCWP (but insensitive) ⁽¹⁾.

- **Crackles/pulmonary edema/pleural effusions.**

Note that crackles are frequently (80%) absent in patients with decompensated chronic HF, even when PCWP is severely elevated. The increased lymphatic drainage of alveolar fluid prevents alveolar pulmonary edema.

- **Peripheral edema ± Ascites**; congestive and sometimes painful hepatomegaly (pulsatile hepatomegaly if severe TR); and rarely, congestive splenomegaly in prolonged failure.

Over 4 liters of volume overload are required to see peripheral edema. Therefore, peripheral edema is an insensitive finding and may be absent in 60% of patients with elevated PCWP; moreover, in many cases, pulmonary edema results from volume redistribution to the lungs rather than fluid volume overload. *Edema is, however, specific for HF in a dyspneic patient.*

The most reliable congestive findings are:

Orthopnea, Elevated JVP, S3, and a recent quick weight gain.

- **Low-output findings:** *(also known as “cold” signs) correlate with a more advanced HF stage.*

- **Severe fatigue, increased time to recover after exercise.**

- **Cold, clammy extremities.**

(1) Mechanism of production:

- **Impact theory**: ventricular filling occurs early in the diastole, if ventricles resist this rapid flow, vibratory activity results which are transmitted to the chest wall.
- **Ventricular theory**: sudden cessation of ventricular filling resulting in distension & vibration of ventricular wall, papillary muscles & chordae.
- **Valvar theory**: sudden limitation of longitudinal expansion of LV wall during diastole

- **Narrow pulse pressure** (< 25% SBP): Since the pulse pressure corresponds to stroke volume, *narrow pulse pressure* (< 25% SBP) implies a low stroke volume. In fact, a narrow pulse pressure is the physical finding that most reliably predicts a low cardiac output (> 85% sensitivity and specificity). Occasionally, severe arterial noncompliance prevents pulse pressure from narrowing.
- **Pulsus alternans (mechanical alternans)**, which refers to an every-other-beat variation in pulse intensity ⁽¹⁾. The pulse must be absolutely regular to distinguish it from the bigeminal pulse, which also has beats of alternating strength, although the rhythm is irregular. In rare cases of pulsus alternans, the weak pulse is so small it is imperceptible, with only half of the beats reaching the radial artery (**total alternans**).
Mechanism: **(1)** based on the Frank-Starling relationship, the end-systolic volume is increased after the weak beat (due to decreased ejection) which leads to a greater end-diastolic volume and more force development in the next beat. **(2)** there is beat-to-beat alternation of myocardial contractility. **(3)** alternation of the intracellular Ca^{2+} transient.
- **Compensatory tachycardia.**
- **Abdominal pain** may result from functional bowel ischemia or from liver distension.
- At an advanced stage: impaired mentation, drowsiness, central hypoventilation with Cheyne–Stokes pattern (hyperpnea alternating with hypopnea/apnea).

Investigations:

▪ Diagnostic tests in all patients with suspected HF:

1. ECG:

- A completely normal ECG almost excludes the diagnosis of HF, particularly systolic HF and acute HF.
- Q waves usually point towards ischemic cardiomyopathy.

(1) This is different from *pulsus paradoxus* and *electrical alternans*. **Pulsus paradoxus**= exaggeration of the normal reduction of SBP during inspiration. Associated conditions include cardiac tamponade, constrictive pericarditis, severe respiratory illness (e.g., asthma, pneumonia), and restrictive cardiomyopathy. **Electrical alternans** is a beat-to-beat variability of the QRS complex on ECG, often found in the setting of pericardial effusion.

- Advanced AV block is frequently seen in myocarditis and infiltrative disease.
- The association of a large QRS voltage in the precordial leads with a low QRS voltage in the limb leads suggests reduced systolic function with dilated LV.
- LBBB with QRS > 130 ms has therapeutic implications (benefit from CRT).

2. B-type natriuretic peptide (BNP):

- BNP is a peptide synthesized in response to cardiomyocyte stretch. Atrial or ventricular wall stress, especially LV wall stress from volume or pressure overload, is the primary driver of BNP secretion, but ischemia and neurohormones may also directly stimulate BNP gene expression.
- Pro-BNP is the precursor of BNP; it is cleaved into BNP and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP).
- BNP takes 1 hour to rise and may be initially normal in hyperacute HF.
- BNP is mostly cleared by tissue peptidase, but is partially cleared renally.
- BNP is lower in obese patients due to increased expression of clearance receptors and augmented peptide degradation by the adipose tissue.
- BNP tends to be higher in the elderly, in women, in AF, in renal failure, and in cirrhosis.
- Diagnostic values apply similarly to HFrEF and HFpEF; on average, values are lower for HFpEF than for HFrEF ⁽¹⁾.
- The upper limit of normal in the **non-acute setting** for [BNP= 35 pg/mL and for NT-proBNP= 125 pg/mL or mid-regional pro-atrial natriuretic peptide (MR-proANP)= 40 pmol/L];
- In the **acute setting**, higher values should be used [BNP= 100 pg/mL, NT-proBNP= 300 pg/ mL and MR-proANP= 120 pmol/L].
 - **BNP > 500 pg/ml** (or NT-pro-BNP > 1200pg/ml) is highly suggestive of acute left HF in a patient with acute dyspnea. It correlates with increased LVEDP.
 - **BNP < 100 pg/ml** (or NT-pro-BNP < 300 pg/ml) excludes acute left HF as a cause of acute dyspnea. The patient may, however, have asymptomatic LV dysfunction or mildly symptomatic LV dysfunction (exertional symptoms). In fact, patients with

(1) For a given filling pressure, dilated ventricles secrete more peptide because of the greater wall stress/stretch and chamber mass. This explains why BNP is higher in LV systolic than in LV diastolic failure, and how it may be high despite a normal LVEDP.

diastolic or even severe systolic dysfunction who do not have overt HF frequently have BNP values that overlap with normal individuals' BNP (BNP <50pg/ml).

- In the acute setting, **BNP levels of 100-500 pg/ml**, (or **35-200 pg/ml** in the chronic setting) are in the intermediate range: Dyspnea may be due to acute left HF, but also to acute pulmonary or pulmonary vascular illness (with RA/RV stretch), or sepsis.

| Table 1-2: Causes of elevated concentration of natriuretic peptides: | |
|--|---|
| Cardiac causes | Non cardiac causes |
| <ul style="list-style-type: none"> - Heart failure - Acute coronary syndromes - Pulmonary embolism - Myocarditis - Left ventricular hypertrophy. - Hypertrophic or restrictive cardiomyopathy - Valvular heart disease - Atrial and ventricular tachyarrhythmia - Heart contusion - Cardioversion, ICD shock - Surgical procedures involving the heart. - Pulmonary hypertension | <ul style="list-style-type: none"> - Advanced age - Ischemic stroke - Subarachnoid hemorrhage - Renal dysfunction - Liver dysfunction (mainly cirrhosis with ascites) - Paraneoplastic syndrome - Chronic obstructive pulmonary disease - Severe infection (including sepsis and pneumonia) - Severe burns - Anemia - Severe metabolic or hormonal abnormalities (e.g thyrotoxicosis, diabetic ketoacidosis) |

N.B:

- ☞ HF induced by mitral stenosis and acute mitral regurgitation has a lower BNP (cases where LVEDP is not necessarily increased).
- ☞ In a patient with clinical HF, JVD, and edema yet normal BNP, consider the diagnosis of constrictive pericarditis.

3. Echocardiography:

HF is a clinical diagnosis. The severity of HF is assessed using the NYHA functional classification.

Echocardiography is done to differentiate the three major categories of HF based on the assessment of EF, also for assessment of valvular function, diastolic dysfunction, and RV function:

- **Assessment of LV systolic function:** For measurement of LVEF, the modified biplane Simpson's rule is recommended. Three-dimensional echocardiography improves the quantification of LV volumes and LVEF and has the best accuracy compared with values obtained through CMR.
- **Assessment of LV diastolic function:** LV diastolic dysfunction is thought to be the underlying pathophysiological abnormality in patients with HFpEF and perhaps HFmrEF, and thus its assessment plays an important role in diagnosis. Although echocardiography is at present the only imaging technique that can allow for the diagnosis of diastolic dysfunction, no single echocardiography variable is sufficiently accurate to be used in isolation to make a diagnosis of LV diastolic dysfunction. Therefore, a comprehensive echocardiography examination is recommended.
- **Assessment of RV function and pulmonary arterial pressure:** Among parameters reflecting RV systolic function, the following measures are of particular importance:
 - TAPSE; abnormal TAPSE < 17 mm indicates RV systolic dysfunction and
 - Tissue Doppler-derived tricuspid lateral annular systolic velocity (s') ($s' < 9.5$ cm/s indicates RV systolic dysfunction).
 - Systolic pulmonary artery pressure is derived from an optimal recording of maximal tricuspid regurgitant jet and the tricuspid systolic gradient, together with an estimate of RA pressure (on the basis of IVC size and its breathing-related collapse).
- **Echo assesses for other forms of HF:**
 - Isolated RV failure with its various causes (e.g., pulmonary hypertension, ASD).
 - Right sided HF mimickers: constrictive pericarditis, tamponade.

4. Chest X-ray:

- It is probably most useful in identifying an alternative, pulmonary explanation for a patient's symptoms and signs (e.g., interstitial lung disease), although CT of the chest is currently the standard of care.
- Pulmonary vascular cephalization ⁽¹⁾, pleural effusion, and perivascular haziness are the most sensitive findings, but X-ray may not show any congestive finding in ~40% of patients with elevated PCWP.
- CT scan is more helpful: interlobular septal thickening is a marker of interstitial pulmonary edema and is highly sensitive and specific for elevated PCWP.
- **Specialized diagnostic tests for selected patients with chronic heart failure:**

5. Cardiac MRI:

- CMR is the gold standard method for the measurements of volumes, mass and EF of both ventricles. It is the best alternative cardiac imaging modality for patients with non-diagnostic echocardiographic studies (particularly for imaging of the right heart) and is the method of choice in patients with complex congenital heart diseases.
- CMR imaging with late gadolinium enhancement (LGE), T1 mapping and extracellular volume will identify myocardial fibrosis/scar. LGE usually implies necrotic or fibrotic tissue, to which gadolinium has a high affinity ⁽²⁾.
- **Cardiac MRI has four major applications in HF:**
 - Assessment of LGE patterns that are specific for some cardiomyopathies (subendocardial or transmural LGE implies ischemic cardiomyopathy, subepicardial or midwall LGE or LGE in a non-coronary distribution implies non-ischemic cardiomyopathy);

(1) Cephalization is defined as a redistribution of blood into the upper lobe vessels and can be diagnosed when the upper lobe veins are the same or larger in diameter relative to the lower lobe veins.

(2) Normally, gadolinium is extracellular and cannot cross the intact cell membranes of the normal myocardium, thereby limiting their distribution volume to the interstitial space. However, in patients with acute myocardial injury, the cell membranes of the affected myocytes have ruptured, and the gadolinium can now also access the 'intracellular' space, leading to an increased distribution volume. Over time, scar tissue forms and the affected myocytes are replaced by a collagen matrix. As a result, the interstitial space is increased and thus also the distribution volume for gadolinium. As various compartments within the myocardium have different wash-in and wash-out kinetics, the gadolinium concentration in these compartments will constantly vary after contrast injection (Gadolinium reaches the normal myocardium soon after injection and cleared rapidly. In contrary, areas of fibrosis are reached and cleared at a much slower rate). The combined effect of reduced wash-in/wash-out kinetics and the increased distribution volume leads to a delayed accumulation of the gadolinium in areas of myocardial injury approximately 10 minutes post-injection.

- Diagnosis of myocarditis in unexplained cardiomyopathy or unexplained, large troponin elevation.
- Diagnosis of infiltrative cardiomyopathy vs. HCM in a patient with thick myocardium (global subendocardial LGE suggests amyloidosis, patchy midwall enhancement suggests HCM).
- Viability assessment in ischemic cardiomyopathy.

6. Coronary angiography: indicated in:

- Patients with HF who suffer from angina pectoris or an 'angina equivalent' despite medical therapy, provided the patient is otherwise suitable for coronary revascularization.
- Patients with a history of symptomatic ventricular arrhythmia or aborted cardiac arrest.
- Patients with HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests in order to establish the ischaemic aetiology and CAD severity.

7. Non-invasive ischemic workup:

- **Single-photon emission CT (SPECT)** can be used to assess myocardial ischaemia and viability, myocardial inflammation or infiltration. Scintigraphy with technetium (Tc)-labelled bisphosphonate has shown high sensitivity and specificity for imaging cardiac transthyretin amyloid.
- **Stress echocardiography:**
 - Exercise or pharmacological stress echocardiography may be used for the assessment of inducible ischaemia in those who are considered suitable for coronary revascularization.

Biphasic response (i.e., an initial increase in contractility at low doses of dobutamine followed by a decrease in contractility at higher levels of stress) suggests that LV is viable and able to increase its contraction, but gets ischemic with high stress.

Uniphasic response with a progressive increase in contractility from lower to higher doses suggests non-ischemic cardiomyopathy **or** ischemic cardiomyopathy related to a coronary stenosis that has been revascularized, but the myocardium has not recovered yet or recovery is prevented by a severe subendocardial scar.

- In patients with unexplained dyspnoea and suspected HFpEF, stress echo help clarify the diagnosis.

- **Coronary CT angiography** is a non-invasive means used to visualize the coronary anatomy in patients with HF with low intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to exclude the diagnosis of CAD, in the absence of relative contraindications.

8. Diastolic stress testing: (used in HFpEF diagnosis)

Chronic dyspnea that is associated with a normal systolic function and no clinical signs of HF may be falsely considered a dyspnea of non-cardiac origin. Diastolic stress testing helps sort out whether dyspnea is due to diastolic dysfunction or to a non-cardiac cause.

These patients may have normal PCWP and PA pressure at rest. However, exertion and the increase in venous return may increase their left-sided filling pressures; also, exertion may markedly increase their blood pressure. This is a masked form of LV diastolic dysfunction that is unveiled with exercise.

A diastolic stress test can be performed with echocardiography, typically using a semi-supine bicycle ergometer exercise protocol with assessment of LV (E/e') and pulmonary artery pressures (TRV), systolic dysfunction (longitudinal strain), stroke volume and cardiac output changes with exercise.

9. Endomyocardial Biopsy (EMB):

Broader application of endomyocardial biopsy is not recommended (due to the limited diagnostic information). For instance, in patients with initially unexplained cardiomyopathy, a specific histologic diagnosis was provided in only 15% of the patients. EMB indicated in 'patients with rapidly progressive HF despite standard therapy' (ESC) or 'when a specific diagnosis is suspected' (ACC/AHA).

| Table 1-3: ESC Recommendations for diagnostic tests in patients with chronic heart failure: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Diagnostic tests in patients with suspected HF: | | |
| The following tests are recommended in all patients with suspected chronic heart failure: | | |
| - BNP/NT-proBNP | I | B |

| | | |
|---|-----|---|
| - 12-lead ECG | I | C |
| - Transthoracic echocardiography | I | C |
| - Chest radiography (X-ray) | I | C |
| - Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin) to differentiate HF from other conditions, to provide prognostic information, and to guide potential therapy | I | C |
| CMR: | | |
| CMR is recommended for: | I | C |
| - assessment of myocardial structure and function in those with poor echocardiogram acoustic windows. | | |
| - characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (myocarditis), LV non-compaction, amyloid, sarcoidosis, iron overload/haemochromatosis. | | |
| CMR with LGE should be considered in DCM to distinguish between ischaemic and non-ischaemic myocardial damage. | IIa | C |
| Invasive coronary angiography (in those who are considered eligible for potential coronary revascularization) | | |
| Invasive coronary angiography is recommended in patients with angina despite pharmacological therapy or symptomatic ventricular arrhythmias. | I | B |
| Invasive coronary angiography may be considered in patients with HFrEF with an intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests. | IIb | B |
| Non-invasive testing: | | |
| CTCA should be considered in patients with a low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis. | IIa | C |

| | | |
|---|------------|----------|
| <i>Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with CAD who are considered suitable for coronary revascularization.</i> | IIb | B |
| <i>Exercise testing may be considered to detect reversible myocardial ischaemia and investigate the cause of dyspnoea.</i> | IIb | C |
| Cardiopulmonary exercise testing: | | |
| <i>Cardiopulmonary exercise testing is recommended as a part of the evaluation for heart transplantation and/or MCS.</i> | I | C |
| <i>Cardiopulmonary exercise testing should be considered to:</i> - Optimize prescription of exercise training. - Identify the cause of unexplained dyspnoea and/or exercise intolerance. | IIa | C |
| Right heart catheterization: | | |
| <i>Right heart catheterization is recommended in patients with severe HF being evaluated for heart transplantation or MCS.</i> | I | C |
| <i>Right heart catheterization should be considered:</i> - When HF is thought to be due to constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states. - Patients with probable pulmonary hypertension, assessed by echo in order to confirm the diagnosis and assess its reversibility before the correction of valve/structural heart disease. | IIa | C |
| <i>Right heart catheterization may be considered in selected patients with HFpEF to confirm the diagnosis</i> | IIb | C |
| EMB: | | |
| <i>EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis, which can be confirmed only in myocardial samples.</i> | IIa | C |

Treatment of HFrEF:

There are three major goals of treatment for patients with HFrEF:

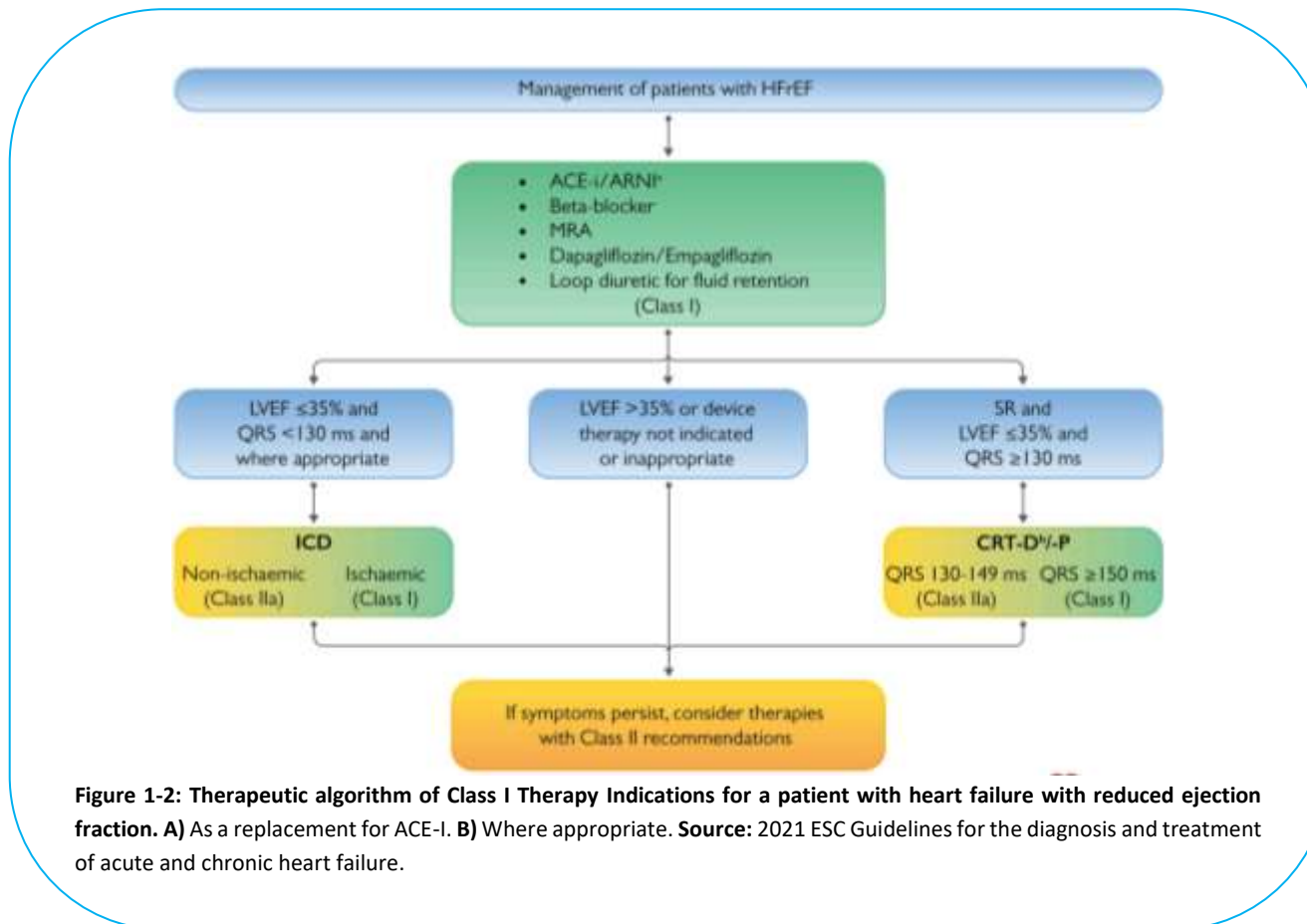
(A) reduction in mortality, **(B)** prevention of recurrent hospitalizations due to worsening HF, and **(C)** improvement in clinical status, functional capacity, and QOL.

Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy, and alongside non-pharmacological interventions.

Three compensatory mechanisms occur in HF and are ultimately harmful:

- 1. LV remodeling** is the process of LV dilatation, LV change in geometry, and LV eccentric hypertrophy that attempt to increase the stroke volume of a hypocontractile myocardium. Over time, however, as the LV undergoes progressive remodeling, it becomes less elliptical and more spherical, progressively more dilated, thin, and fibrotic, with increased wall stress (afterload); all this ultimately decreases the stroke volume. LV end-systolic volume is the best measurement of LV remodeling. EF, often considered a contractility index, is affected by preload and afterload and is, in fact, more a remodeling index than a contractility index.
- 2. Increased activity of the sympathetic system** increases cardiac contractility but ultimately exhausts the myocardium, makes it less responsive to catecholamines, and promotes apoptosis.
- 3. Increased activity of RAAS** elicits vasoconstriction and increases blood volume. This aims to maintain the blood pressure and the kidney perfusion, but is deleterious to the LV.

Modulation of the RAAS and sympathetic nervous systems with ACE-I or ARNI, beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). Added to this triple therapy, sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g dapagliflozin and empagliflozin) reduced the risk of CV death and worsening HF in patients with HFrEF.



▪ Pharmacological Treatment:

1. ACE-I or ARB:

- ACE-Is were the first class of drugs shown to reduce mortality and morbidity and improve symptoms in patients with HFrEF.
- ACE-Is and ARBs increase cardiac output, reduce LV remodeling, and improve EF. ACE-Is have been shown to improve symptoms and exercise capacity, reduce the risk of HF hospitalization (by ~30%), and reduce mortality (by ~20%) in patients with HFrEF.

ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, hospitalization and death.

- ARBs are recommended for patients who cannot tolerate ACE-I or ARNI because of cough or angioedema. The main ARBs studied in HF are *candesartan*, *losartan* and *valsartan*. Candesartan in the CHARM-Alternative study reduced CV deaths and HF hospitalizations in patients who were not receiving an ACE-I. Valsartan, in addition to usual therapy, including ACE-I, reduced HF hospitalizations in the Val-HeFT trial. However, no ARB has reduced all-cause mortality in any trial.
- The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.
- **How to use?**
 - Start with a low dose, then Double the dose at not less than 2-week intervals in the community. More rapid dose uptitration may be carried out in patients in hospital.
 - Aim for the target dose or, failing that, the highest tolerated dose [remember: some ACE-I (or ARB) is better than no ACE-I].
 - Re-check blood chemistry (urea, creatinine, K⁺) 1-2 weeks after initiation or after final dose titration. Monitor blood chemistry 4-monthly thereafter.
- **Be cautious in cases of:**
 - Hypotension with SBP < 80 mmHg or with symptoms of low output (dizzy, obtunded, oliguric). A low SBP of 80-90 mmHg may be well tolerated in HF because it helps unload the LV; ACE-I is started slowly and the diuretic is reduced if possible.
 - Elevation of creatinine of over 50% within 1-2 weeks of ACE-I/ARB initiation. An increase in creatinine of up to 50% above baseline, or 3 mg/dL, or eGFR > 25 mL/min/1.73 m², whichever is the smaller, is acceptable ⁽¹⁾. An increase in K⁺ to ≤ 5.5 mmol/L is also acceptable.
 - If urea, creatinine, or K⁺ does rise excessively:
 - ☞ Consider stopping nephrotoxic drugs (e.g. NSAIDs) and other K⁺ supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic.

(1) In fact, in one study, patients with early worsening of renal function appeared to derive the largest benefit from ACE-I.

- ☞ If greater rises in creatinine or K^+ persist, the dose should be halved and blood chemistry re-checked within 1-2 weeks; if still unsatisfactory response, specialist advice should be sought.
- ☞ If K^+ rises to > 5.5 mmol/L or creatinine increases by $> 100\%$ or to > 3.5 mg/dL or eGFR < 20 mL/min/ 1.73 m², the ACE-I (or ARB) should be stopped, and specialist advice sought.
- ☞ Bilateral renal artery stenosis may need to be ruled out.
- Avoid starting ACE-I in clinically decompensated HF or acute renal failure, because ACE-I may acutely worsen kidney perfusion and the diuretic response. However, if the patient was already on an ACE-I before HF decompensation, the ACE-I is usually continued unless severe, acute renal failure is present.

2. β -Blockers:

- β -Blockers used to be contraindicated in HF due to their initial negative inotropic effect. In fact, they may worsen HF initially, especially in the first 2-3 months after therapy initiation and/or up-titration. But when used over the long term, β -blockers:
 - Improve contractility, EF (by 5-15%), HF symptoms, and reduce mortality by 35-60% and HF hospitalizations by 40%.
 - Reverse the deleterious and apoptotic effects of catecholamines on the heart.
 - Reverse remodeling and reduce cardiac chamber size by reducing LV wall stress.
 - Prevent arrhythmias.
- Beta-blockers are recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of death.
- The three agents that have been shown to improve survival and outcomes in HF are:
 - A. Bisoprolol:** a selective β_1 -blocker.
 - B. Metoprolol:** metoprolol is a selective β_1 -blocker, but loses selectivity with high doses > 100 mg.
Long-acting metoprolol has a more sustained effect than regular metoprolol; this limits the daily fluctuations of the β -blocker that occurs between the doses of regular metoprolol.
 - C. Carvedilol:** non-selective β_1 -blocker, β_2 -blocker, and α_1 -blocker (vasodilatory effect), with additional antioxidant properties. Despite its α -blocker effect, it is as well tolerated as metoprolol in patients with borderline BP.

Carvedilol improves myocardial function, EF, and cardiac hemodynamics such as stroke volume, PA pressure, and PCWP, more than other β -blockers and reverses remodeling more effectively (more comprehensive blockade of all adrenergic receptors) ⁽¹⁾.

Because of the α -blocking effect, carvedilol acts as a moderate vasodilator acutely, but with long-term treatment the vasodilator activity is no longer prominent, as tolerance to the α -blocking effect occurs. This transient α -blocker effect is useful, as it allows an early improvement in stroke volume.

- **Keys to β -blocker therapy:**

- *Start "low and slow"*: Patients have to be euvolemic and stable.
- Double the dose every 2 weeks and monitor for worsening of dyspnea, edema, weight gain, bradycardia, and hypotension.
- If the patient is off the β -blocker for over 1 week for any reason, or after an episode of cardiogenic shock, restart at the lowest dose and retitrate.

- There is consensus that ACE-I and beta-blockers can be commenced. There is no evidence favouring the initiation of a beta-blocker before an ACE-I and vice versa.
- If the patient has been on a β -blocker for more than a few weeks and is hospitalized with HF decompensation, the β -blocker should not generally be withheld. In low-output HF decompensation with borderline BP, the β -blocker dosage may be reduced. In full-blown shock, the β -blocker is withheld.

3. Aldosterone receptor antagonists (Spironolactone, Eplerenone)

- The high aldosterone levels seen in HF not only induce renal sodium retention but directly act on the myocardial and arterial aldosterone receptors, leading to myocardial and arterial remodeling and fibrosis and baroreceptor dysfunction.
- The benefit in HF mainly results from:
 - Blockade of the myocardial aldosterone receptors;

(1) *The non-selective blockade of adrenergic receptors is advantageous. While metoprolol upregulates β -receptor density towards normal levels, carvedilol maintains a low density of these receptors. Moreover, selective β_1 -blockade with metoprolol may enhance the ino- and chronotropic response to β_2 -adrenergic stimulation, an untoward effect. Thus, carvedilol is a more potent antiadrenergic agent than metoprolol, as manifested by the more significant blunting of heart rate response.*

- Increase in potassium (antiarrhythmic effect);
- Reduction of the tubular resistance to loop diuretics.
- An aldosterone receptor antagonist is indicated in chronic HF with EF \leq 35% and NYHA classes III-IV. It is also indicated after a recent ACS (within 30 days) when EF $<$ 40% and clinical HF or diabetes is present.
- If gynecomastia develops, eplerenone may be used instead of spironolactone.
- **How to use:**
 - Start with a low dose and consider dose up-titration after 4-8 weeks.
 - Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter.
 - ☞ If K⁺ rises above 5.5 mmol/L or creatinine rises to 2.5 mg/dL or eGFR $<$ 30 mL/min/1.73 m², halve a dose and monitor blood chemistry closely.
 - ☞ If K⁺ rises to $>$ 6.0 mmol/L or creatinine to $>$ 3.5 mg/dL or eGFR $<$ 20 mL/min/1.73 m², stop MRA immediately and seek specialist advice.

4. Angiotensin Receptor Neprilysin Inhibitor (ARNI) (Sacubitril–Valsartan):

- Sacubitril is neprilysin inhibitor, so inhibiting the degradation of natriuretic peptides (NPs), bradykinin. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP:
 - Enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling.
 - Inhibiting renin and aldosterone secretion.
 - Selective Angiotensin type 1 (AT1)-receptor blockade reduces sodium and water retention and myocardial hypertrophy.
- Neprilysin inhibitor + valsartan was associated with less renal dysfunction and hyperkalemia than ACE-I, but more symptomatic hypotension.
- To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan.

- Patients being commenced on sacubitril/valsartan should have an adequate blood pressure, and an eGFR ≥ 30 mL/min/1.73 m².
- A prior history of angioedema with ACE-I contraindicates the use of sacubitril/valsartan, but a prior history of cough is not a contraindication.
- Of note, sacubitril is the only HF therapy that increases BNP, a consequence of its direct effect. This affects the diagnostic value of BNP, at least during therapy initiation, but BNP remains useful for monitoring in respect to the new baseline. Conversely, NT-pro-BNP is not directly affected.
- **How to use:**
 - Start with a low dose.
 - In some patients, one may consider a reduced starting dose (24/26 mg b.i.d.), namely in those with SBP 100-110 mmHg, ACE-I/ARB naive patients, eGFR 30-60 mL/min/1.73 m².
 - Double the dose at not less than 2-week intervals in the community, monitoring tolerability.
 - Re-check blood chemistry (urea/BUN, creatinine, K⁺) 1-2 weeks after initiation and after final dose titration. Monitor blood chemistry 4-monthly thereafter.

5. Sodium-glucose co-transporter 2 inhibitors:

- Dapagliflozin or empagliflozin are recommended, in addition to ACE-I/ARNI, beta-blocker and MRA, for patients with HFrEF regardless of diabetes status to improve QOL, to prevent HF hospitalization, and to reduce the risk of CV and all-cause deaths.
- The diuretic/natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.
- The combined SGLT-1 and 2 inhibitor, sotagliflozin, has also been studied in patients with diabetes who were hospitalized with HF. The drug reduced CV death and hospitalization for HF.
- Therapy with SGLT2 inhibitors may increase the risk of recurrent genital fungal infections. A small reduction in eGFR following initiation is expected and is reversible and should not lead to premature discontinuation of the drug.
- **How to use:**

- Check renal function when starting the therapy and monitor regularly. eGFR is known to dip slightly after initiation but the SGLT2 inhibitors appear to be reno-protective.
- Monitor glycaemia, particularly in diabetic patients. Consider modification of other diabetic drugs.
- Identify the risk factors predisposing to ketoacidosis and eliminate them if possible.
- Monitor fluid balance regularly. Consider an adjustment of diuretic therapy and fluid intake.

6. Diuretics:

- Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects on mortality and morbidity have not been studied in RCTs.
- Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema. However, adverse effects are more likely and these combinations should only be used with care.
- Loop diuretic resistance is generally due to a series of renal adaptations after diuretic use ('braking phenomenon') including **(i)** hypertrophy and hyperfunction of other sites of the nephron causing sodium reabsorption, **(ii)** increased renin secretion in the macula densa, and **(iii)** reduced diuretic delivery to the the diuretic's tubular site of action (due to to hypoalbuminemia and increased organic ions).
- Patients can be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.
- **How to use?**
 - Check renal function and electrolytes, particularly in those on loop and thiazide diuretics combination.
 - Start with a low dose but target an effective dose for a patient to achieve diuresis with a simultaneous reduction of body weight by 0.75-1.0 kg per day.
 - Re-check (Urea, creatinine, K⁺) 1-2 weeks after an initiation and after any increase in dose.
- **Insufficient diuretic response/diuretic resistance:**
 - Check adherence and fluid/salt intake.

- Increase a dose of diuretic.
- Consider switching from furosemide to bumetanide or torasemide.
- Add an MRA/increase dose of an MRA.
- Combine loop diuretic and thiazide/metolazone.
- Administer loop diuretic twice (or more times) daily or on empty stomach.
- Consider short-term i.v. infusion of loop diuretic.
- Consider ultrafiltration.

7. I_f-channel inhibitor:

- Ivabradine slows the heart rate through inhibition of the I_f channel in the sinus node and therefore should only be used for patients in sinus rhythm.
- Ivabradine reduced the combined endpoint of mortality or hospitalization for HF in patients with symptomatic HFrEF or LVEF ≤ 35%, in sinus rhythm and with a heart rate ≥ 70 bpm receiving treatment with a maximum tolerated dose of beta-blocker, ACEI/ARB and MRA (SHIFT trial) ⁽¹⁾.

8. Hydralazine-nitrate combination:

- The V-HeFT-I trial was the first trial ever to show a mortality reduction with vasodilator therapy in HF. The mortality reduction was mainly in *black patients*. Therefore, the combination is indicated as an additional therapy to ACE-I/ARB and β blocker in black patients with NYHA class III–IV.
- The combination may also be used instead of ACE-I/ARB in case of intolerance to ACE-I/ARB.
- The benefit is partly related to the afterload and preload reduction. More importantly, nitrates increase the local production of nitric oxide (NO), while hydralazine prevents the oxidation of NO through its antioxidant properties, allowing to maintain the NO effect. NO promotes endothelial and vascular homeostasis and appropriate myocardial remodeling and contractility, which improves EF by up to 5%.

(1) European Medicines Agency (EMA) approved ivabradine for use in patients with HFrEF with LVEF ≤ 35% and in SR with resting heart rate ≥ 75 b.p.m. because in this group, ivabradine conferred a survival benefit based on retrospective subgroup analysis.

- Hydralazine-nitrate combination may also directly reduce pulmonary vascular resistance in patients with left HF-associated pulmonary hypertension.

9. Vericiguat:

- In HF, there is a change in nitric oxide synthesis as well as a decrease in the activity of its receptor, soluble guanylate cyclase (GC), which in turn causes cyclic guanosine monophosphate (cGMP) deficiency. The cGMP deficiency causes deterioration in myocardial, vascular, and renal function.
- Vericiguat is an oral drug that directly stimulates GC, which increases the availability of intracellular cGMP and thus produces beneficial effects, including a reduction in LV remodeling, an improvement in myocardial and vascular function, and a decrease in fibrosis and inflammation.
- Vericiguat should be considered in symptomatic patients who present with worsening of HF despite first-line treatment to reduce the risk of CV death or hospitalization due to HF (VICTORIA Trial) ⁽¹⁾.

10. Other treatments with less certain benefits:

- **Digoxin:**

- Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce both all-cause and HF hospitalizations, but the overall effect on mortality was neutral (DIG trial).
- In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, when other therapeutic options cannot be pursued.
- Digoxin has a narrow therapeutic window and so levels should be checked aiming for a serum digoxin concentration < 1.2 ng/mL. Caution should be exercised when using it in females, the elderly, frail, and hypokalaemic subjects. In patients with reduced renal function, digitoxin could be considered.

(1) Note that, unlike other drugs that inhibit certain deleterious pathways that are activated, such as the RAAS or the sympathetic nervous system, vericiguat and sacubitril stimulate the protective pathways (nitric oxide-GC-GMP system and natriuretic peptides, respectively).

- **n-3 polyunsaturated fatty acids:** n-3 PUFA preparations differ in composition and dose. Only preparations with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethyl esters of at least 85% (850 mg/g) have shown an effect on the cumulative endpoint of CV death and hospitalization.

- **Cardiac myosin activator (Omecamtiv mecarbil):**

Omecamtiv mecarbil is a selective cardiac myosin activator, which binds to the catalytic domain of myosin ⁽¹⁾. This enhances effective actin-myosin cross-bridge formation and creates a force-producing state that is not associated with cytosolic calcium accumulation.

The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF.

Table 1-4: Evidence-based doses of drugs used in HFrEF or after MI:

| | Starting dose (mg) | Target dose (mg) |
|------------------------------|--------------------|------------------|
| ACE-I | | |
| <i>Captopril</i> | 6.25 t.i.d. | 50 t.i.d. |
| <i>Enalapril</i> | 2.5 b.i.d. | 10–20 b.i.d. |
| <i>Lisinopril</i> | 2.5–5.0 o.d. | 20–35 o.d. |
| <i>Ramipril</i> | 2.5 o.d. | 10 o.d. |
| <i>Trandolapril</i> | 0.5 o.d. | 4 o.d. |
| Beta-blockers | | |
| <i>Bisoprolol/ Nebivolol</i> | 1.25 o.d. | 10 o.d. |

(1) Cardiac myosin is the cytoskeletal motor protein found in the cardiomyocyte, which is directly responsible for converting the chemical energy to mechanical force, leading to the heart's contraction.

| | | |
|---|-----------------------------|-----------------------------------|
| <i>Carvedilol</i> | 3.125 b.i.d. | 25 b.i.d. (50 b.i.d. if BW> 85kg) |
| <i>Metoprolol succinate (CR/XL)</i> | 12.5–25 o.d. | 200 o.d. |
| ARBs | | |
| <i>Candesartan</i> | 4–8 o.d. | 32 o.d. |
| <i>Valsartan</i> | 40 b.i.d. | 160 b.i.d. |
| <i>Losartan</i> | 50 o.d. | 150 o.d. |
| MRAs ⁽¹⁾ | | |
| <i>Eplerenone</i> | 25 o.d. | 50 o.d. |
| <i>Spironolactone</i> | 25 o.d. ⁽²⁾ | 50 o.d. |
| ARNI | | |
| <i>Sacubitril/valsartan</i> | 49/51 b.i.d. ⁽³⁾ | 97/103 b.i.d. |
| SGLT2 inhibitors: | | |
| <i>Dapagliflozin</i> | 10 mg o.d. | 10 mg o.d. |
| <i>Empagliflozin</i> | 10 mg o.d. | 10 mg o.d. |
| I_f-channel blocker | | |
| <i>Ivabradine</i> | 5 b.i.d. | 7.5 b.i.d. |
| Hydralazine–nitrate: | | |
| <i>Hydralazine–isosorbide dinitrate</i> | 12.5/20 t.i.d | 50/40 t.i.d |
| Soluble Guanylate cyclase activator: | | |

(1) In cirrhosis, a high dose of spironolactone (100-400 mg) has been shown to induce more natriuresis than a loop diuretic. In fact, the avid distal sodium reabsorption induced by hyperaldosteronism makes loop diuretics ineffective in 50% of cirrhotic patients.

(2) Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

(3) Sacubitril/valsartan may have optional lower starting dose of 24/26 mg b.i.d. for those with a history of symptomatic hypotension. **Dose in children < 40 kg:** a starting dose of 1.6 mg/kg titrated to a maximum of 3.1 mg/kg has been suggested.

| | | | | |
|-------------------------------------|-------------|-------------|-------------|-------------|
| Vericiguat | 2.5 mg o.d | 10 mg o.d | | |
| Glycosides: | | | | |
| Digoxin | 62.5 µg o.d | 250 µg o.d | | |
| Diuretics: | | | | |
| Loop diuretics: | | | | |
| Furosemide | 20-40 | 40-240 | | |
| Butanamide | 0.5-1 | 1-5 | | |
| Torsemide | 5-10 | 10-20 | | |
| Thiazides: | | | | |
| Bendroflumethiazides | 2.5 | 2.5-10 | | |
| Hydrochlorothiazides | 25 | 12.5-100 | | |
| Metolazone | 2.5 | 2.5-10 | | |
| Indapamide | 2.5 | 2.5-5 | | |
| Potassium-sparing diuretics: | | | | |
| | + ACEI/ARBs | - ACEI/ARBs | + ACEI/ARBs | - ACEI/ARBs |
| Spironolactone/Eplereonone | 12.5-25 | 50 | 50 | 100-200 |
| Amiloride | 2.5 | 5 | 5-10 | 10-20 |
| Triametrene | 25 | 50 | 100 | 200 |

Table 1-5: ESC Recommendations for Pharmacological treatments indicated in patients with (NYHA class II–IV) HFrEF (LVEF ≤ 40%):

| Recommendations | Class | Level |
|--|--------------|--------------|
| Pharmacological treatments indicated in patients with (NYHA class II-IV) HFrEF: | | |

| | | |
|---|------------|----------|
| <i>An ACE-I, beta-blocker, MRA and dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.</i> | I | A |
| <i>Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.</i> | I | B |
| Other pharmacological treatments indicated in selected patients with (NYHA class II-IV) HFrEF: | | |
| Loop diuretics: | | |
| <i>Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.</i> | I | C |
| ARB: | | |
| <i>An ARB⁽¹⁾ is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta blocker and an MRA).</i> | I | B |
| If-channel inhibitor: | | |
| <i>Ivabradine should be considered in symptomatic patients with LVEF ≤ 35%, in SR and a resting heart rate ≥ 70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.</i> | IIa | B |
| <i>Ivabradine should be considered in symptomatic patients with LVEF ≤ 35%, in SR and a resting heart rate ≥ 70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.</i> | IIa | C |
| Soluble guanylate cyclase stimulator: | | |

(1) The ARBs with evidence in HFrEF are candesartan, losartan, and valsartan.

| | | |
|--|------------|----------|
| <i>Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.</i> | IIb | B |
| Hydralazine and isosorbide dinitrate: | | |
| <i>Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF \leq 35% or with an LVEF $<$ 45% combined with dilated LV in NYHA class III-IV despite treatment with ACE-I (or ARNI), beta-blocker and an MRA to reduce the risk of HF hospitalization and death.</i> | IIa | B |
| <i>Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACE-I, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.</i> | IIb | B |
| Digoxin: | | |
| <i>Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).</i> | IIb | B |

▪ **Device Treatment:**

1. Implantable Cardioverter Defibrillator (ICD):

- 50% of patients with HF die of VT or VF. The remaining 50% of patients die of end-stage, low-output HF. ICDs are effective at correcting potentially lethal ventricular arrhythmias ⁽¹⁾, and in the case of transvenous systems, also prevent bradycardia.
- **As a primary prevention, ICD is indicated in patients with cardiomyopathy and EF $<$ 35%:**
 - Wait $>$ 40 days after MI. RCTs showed no benefit of ICD implantation within 40 days after a MI.

(1) Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, but they do not reduce overall mortality (as in amiodarone), and may increase it (as in dronedarone and the class I antiarrhythmic agents disopyramide, encainide, and flecainide).

- Wait > 3 months after revascularization for chronic ischemia.
 - Wait 3-6 months in non-ischemic cardiomyopathy, to ensure that it is not reversible and that it persists after a few months of medical therapy.
- Patients with functional class IV have a higher risk of VT/ VF than other functional classes, they also have a much higher risk of death from pump failure; ICD simply converts their mode of death from VT to pump failure. Thus, ICD therapy is not recommended in patients in NYHA class IV, with severe symptoms refractory to pharmacological therapy, who are not candidates for LV assist device or heart transplant.
 - Similarly, patients with serious comorbidities who are unlikely to survive substantially more than 1 year with good QOL are unlikely to obtain substantial benefit from an ICD.
 - On average, patients with IHD are at greater risk of sudden death than patients with DCM and therefore, although the relative benefits are similar, the absolute benefit is greater in patients with IHD.
 - Patients should be counselled to the purpose of an ICD, complications related to implantation and device activation (predominantly inappropriate shocks) and under what circumstances it might be deactivated (terminal disease) or explanted (infection).
 - Generally, for primary prevention, ICDs are programmed to minimize pacing (e.g., ventricular demand pacing VVI at 40/min), and with a tachycardia treatment zone > 200/min.
 - Subcutaneous ICDs (S-ICDs) appear to be as effective as conventional transvenous ICDs with a similar complication rate. They may be the preferred option for patients with difficult venous access or those who require ICD explantation due to infection. Patients must be carefully selected, as S-ICDs cannot treat bradyarrhythmia (except post-shock pacing) and cannot deliver either anti-tachycardia pacing or CRT.

Table 1-6: ESC Recommendations for implantable cardioverter defibrillator in patients with heart failure:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------------|--------------|--------------|
| Secondary prevention: | | |

| | | |
|---|------------|----------|
| <i>ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for > 1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred < 48 h after a MI.</i> | I | A |
| Primary prevention: | | |
| <i>ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days), and an LVEF \leq 35% despite \geq 3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.</i> | I | A |
| <i>ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of a non-ischaemic aetiology, and an LVEF \leq 35% despite \geq 3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.</i> | IIa | A |
| <i>Patients should be carefully evaluated by experienced cardiologist before generator replacement, because management goals, the patient's needs and clinical status may have changed. (Risk of fatal arrhythmia may be lower, or the risk of non-arrhythmic death may be higher)</i> | IIa | B |
| <i>A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.</i> | IIb | B |
| <i>ICD implantation is not recommended within 40 days of a MI as implantation at this time does not improve prognosis</i> | III | A |
| <i>ICD therapy is not recommended in patients in NYHA class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a VAD, or cardiac transplantation.</i> | III | C |

2. Cardiac Resynchronization Therapy (CRT):

- CRT (also called biventricular pacemaker, BiV PM), is a pacemaker that typically has three leads: RA lead, RV lead, and LV epicardial lead placed via the coronary sinus. In a way, it is a DDD PM with an additional LV lead inserted percutaneously via the coronary sinus into the left lateral vein or surgically onto the lateral left ventricular wall.
- Approximately 20-30% of HF patients have QRS > 120 ms, mostly LBBB (80%). This leads to dyssynchronous contraction of the LV, which means that different LV segments contract at different times (intraventricular dyssynchrony), and the LV and RV contract at different times (interventricular dyssynchrony) and dyssynchronous mitral leaflets movement (→ MR). This leads to ineffective systolic function, as one wall contracts while the other stretches in the opposite direction, a reduction in stroke volume, a larger LV volume in systole, and subsequently, a maladaptive LV dilatation.
- CRT improves survival, symptoms, and EF. It decreases LV systolic size (= reverse remodeling) and reduces functional MR (the two leaflets coapt at the same time when all segments contract simultaneously).
- CRT improves diastolic function as it reduces systolic time, thus increasing the diastolic filling time. It leads to immediate improvement of symptoms, then reverse remodeling within months.
- To be beneficial, it has to track the atrial rate and pace both ventricles ~100% of the time. It cannot be in a standby mode.

Table 1-7: ESC Recommendations for Indications of CRT:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| In HFrEF patients with sinus rhythm: | | |
| <i>For symptomatic patients with HF in SR with LVEF ≤ 35%,</i> | | |
| - CRT is recommended if QRS duration ≥ 150 ms, and LBBB QRS morphology. | I | A |
| - CRT should be considered if QRS duration 130-149 ms, and LBBB QRS morphology. | IIa | A |

| | | |
|--|------------|----------|
| <i>despite OMT, in order to improve symptoms and reduce morbidity and mortality.</i> | | |
| <i>For symptomatic patients with HF in SR with LVEF ≤ 35%,</i> | | |
| - CRT should be considered if QRS duration ≥ 150 ms, and non-LBBB QRS morphology | Ila | B |
| - CRT may be considered if QRS duration 130-149 ms, and non-LBBB QRS morphology | Ilb | B |
| <i>despite OMT, in order to improve symptoms and reduce morbidity.</i> | | |
| <i>CRT is not indicated in patients with HF and QRS duration < 130 ms without an indication for RV pacing.</i> | III | A |
| In patients with AF: | | |
| <i>CRT should be considered for patients with HF and LVEF ≤ 35% in NYHA class III or IV despite OMT if they are in AF and have intrinsic QRS ≥ 130 ms, provided a strategy to ensure biventricular capture is in place, in order to improve symptoms and reduce morbidity and mortality.</i> | Ila | C |
| <i>AVJ ablation should be added in case of incomplete biventricular pacing (< 90-95%) due to conducted AF.</i> | Ila | B |
| <i>If AV nodal ablation and pacing are performed to control the AF rate ⁽¹⁾:</i> | | |
| A) CRT is recommended in patients with HFrEF. | I | B |
| B) CRT rather than standard RV pacing should be considered in patients with HFmrEF. | Ila | C |
| C) RV pacing should be considered in patients with HFpEF. | Ila | B |
| D) CRT may be considered in patients with HFpEF. | Ilb | C |
| For Antibradycardic pacing: | | |
| <i>CRT (rather than RV pacing) is recommended for patients with HFrEF (< 40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.</i> | I | A |

(1) AF ablation has been reported to improve LVEF and reduce the HF hospitalization rate, particularly when tachycardia-induced cardiomyopathy is highly probable.
 CRT should be considered in those patients with persistent AF and HFrEF when AF ablation cannot be performed or is declined by the patient.

Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF \leq 35% despite OMT, and who have a significant proportion of RV pacing ⁽¹⁾, should be considered for upgrade to CRT.

Ila

B

3. Cardiac contractility modulation (CCM) is similar in its mode of insertion to CRT, but it involves applying relatively high-voltage (≈ 7.5 V), long-duration (≈ 20 ms), biphasic electric signals to the RV septal wall during the absolute refractory period to enhance contractile performance without activating extra systolic contractions (non-excitatory electrical stimulation).

CCM has been evaluated in patients with NYHA class III-IV HF, with an LVEF 25-45% and QRS duration < 130 ms, and was associated with a small improvement in exercise tolerance and QOL.

▪ **Other therapeutic measures:**

- **Salt restriction:** avoid high salt intake > 6 g NaCl/day (= 2.4 g Na). Average salt intake in the western world is 6-8 g.
- **Fluid restriction** to 1.5-2 liters/day is necessary in advanced HF, decompensated HF, or hyponatremia.
- **Exercise training** in stable HF. Exercise training improves vascular function, muscular O₂ extraction, and symptoms.
- **Iron therapy.** In HF, higher cutoffs of ferritin are used to define iron deficiency, as some iron is misused and blocked in the reticuloendothelial system (ferritin < 100 , or 100-300 with iron saturation $< 20\%$).
Intravenous iron therapy improved walking distance and NYHA class and reduced HF hospitalizations (CONFIRM-HF trial). Conversely, erythropoietin therapy did not provide any benefit.
- **Omega-3 fatty acids:** small dose of 1 g/day, have been shown to slightly reduce mortality in class II–IV HF with any EF (GISSI-HF trial).
- **Avoidance of harmful medications:**
 - Anti-inflammatory medications: Glucocorticoids (sodium retention), NSAIDs (sodium retention and peripheral vasoconstriction; blunted response to diuretics and ACE-Is).

(1) A limit of 20% RV pacing for considering interventions for pacing-induced HF is supported by observational data.

- Antiarrhythmic medications: Class I antiarrhythmic agents (negative inotropy; proarrhythmia; increased mortality with IA and IC agents in post-MI trials), Class III antiarrhythmic agents (e.g sotalol and ibutalide; Proarrhythmia).
- Non-dihydropyridines CCBs (negative inotropic effect) ⁽¹⁾.
- Diabetes medications: Thiazolidinediones (sodium retention).
- Anagrelide (selective thrombocytopenic drug; tachycardia, sodium retention, HF induction/exacerbation)
- Cilostazol (antiplatelet drug and a vasodilator; ventricular tachyarrhythmias).
- Neurologic and psychiatric medications: Amphetamines (sympathetic agonist activity; hypertension; tachycardia; tachyarrhythmias), Carbamazepine (negative inotropic effect; bradyarrhythmias), Tricyclic antidepressants (negative inotropic effect; proarrhythmia).
- Licorice (mineralocorticoid excess; sodium retention and hypokalemia).

(1) Dihydropyridines are not contraindicated, with the exception of nifedipine, which has a mild negative inotropic effect

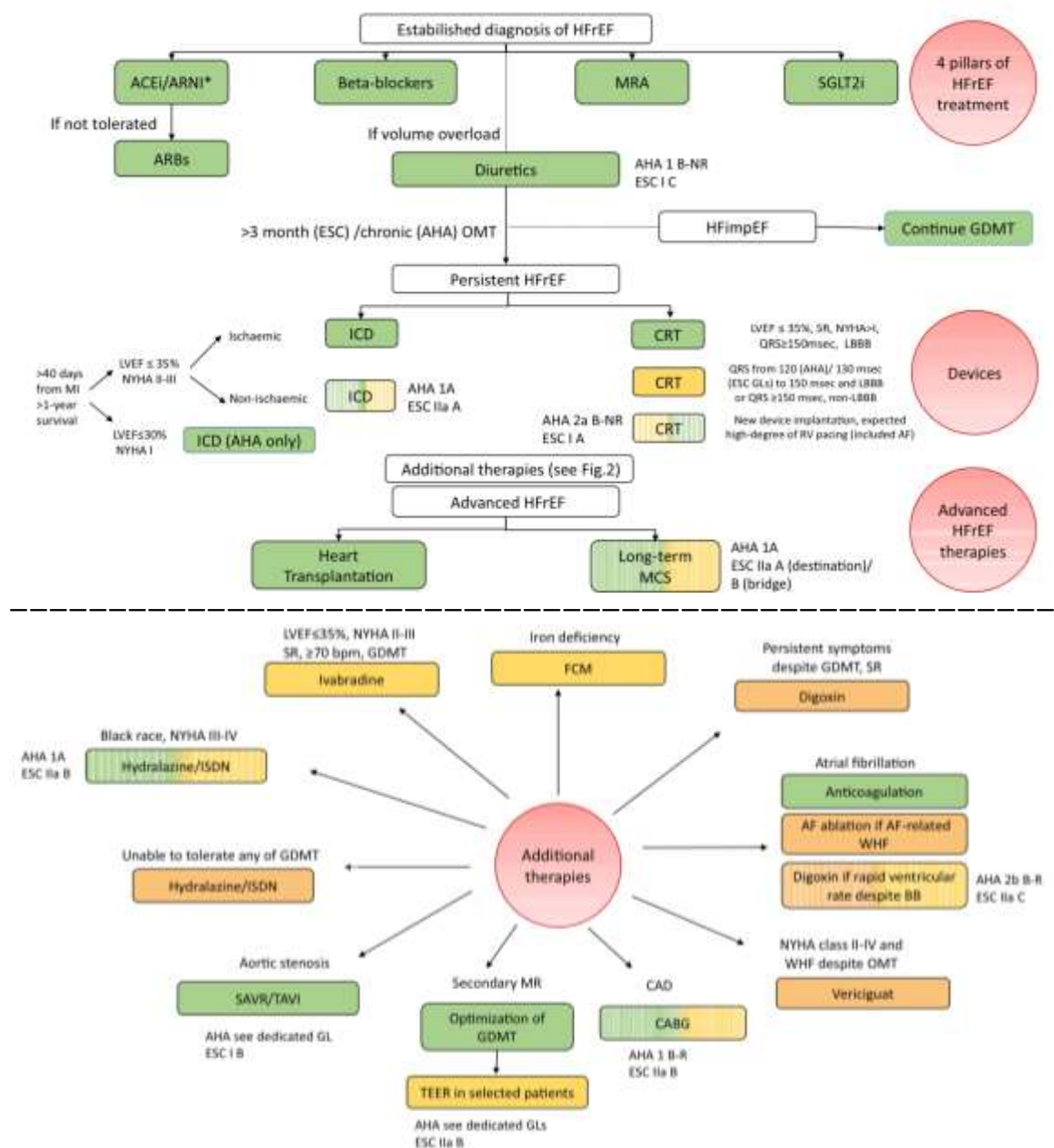


Figure 1-3: Management of HFrEF: a comparison between ACC/AHA/HFSA and ESC guidelines. *The recommendation for ARNI in patients receiving ACEi is I B in both ACC/AHA and ESC guidelines. ACC/AHA/HFSA guidelines recommend ARNI as first line therapy. **Source:** Tomasoni D, Adamo M, Bozkurt B, et al. Aiming at harmony. Comparing and contrasting international HFrEF guidelines. European Heart Journal Supplements. 2022 Dec 27;24(Supplement_L):L20-8.

Prognosis:

- The average yearly mortality of patients with class II or III HF is ~ 6-10%. Half of deaths are sudden deaths, the other half are pump failure deaths. MI contributes to 30-50% of each death modality in ischemic HF.
- Despite receiving less evidence-based treatment, women have a better survival than men, but with higher rates of hospitalizations.
- **Predictors of HF hospitalizations:** AF, higher BMI, higher HbA1c, and low eGFR.
- **Several factors negatively affect prognosis in HF patients:**
 - Severely decreased EF (< 30%).
 - Refractory functional class IIIB or IV (1-year mortality 30-50%).
 - Hospitalization for decompensated HF is associated with a high mortality, especially in the first few months after hospitalization (4- to 10-fold higher mortality). The risk progressively decreases throughout the ensuing 12 months, but does not reach the level of risk of the patient without HF hospitalization.
 - Low-output profile, i.e., hypotension, resting tachycardia, cachexia, renal failure, poor response to diuretics, hyponatremia < 133 mmol/l, anemia of HF with Hb < 12 g/dl.
 - Borderline BP < 100 mmHg with inability to tolerate ACE-I and/or β -blocker therapy, or a need to discontinue them in hypotensive, low-output states.

Prevention of heart failure:

Table 1-8: Risk factors for the development of heart failure and potential corrective actions:

| Risk factors for heart failure | Preventive strategies |
|--------------------------------|---|
| Sedentary habit | <i>Regular physical activity</i> |
| Cigarette smoking | <i>Cigarette smoking cessation</i> |
| Obesity | <i>Physical activity and healthy diet</i> |

| | |
|--|--|
| Excessive alcohol intake | <i>General population: no/light alcohol intake is beneficial. Patients with alcohol-induced CMP should abstain from alcohol.</i> |
| Influenza | <i>Influenza vaccination</i> |
| Microbes (e.g. Trypanosoma cruzi) | <i>Early diagnosis, specific antimicrobial therapy for either prevention and/or treatment</i> |
| Cardiotoxic drugs (e.g., anthracyclines) | <i>Cardiac function and side effect monitoring, dose adaptation, change of chemotherapy</i> |
| Chest radiation | <i>Cardiac function and side effect monitoring, dose adaptation</i> |
| Hypertension | <i>Lifestyle changes, antihypertensive therapy</i> |
| Dyslipidaemia | <i>Healthy diet, statins</i> |
| Diabetes mellitus | <i>Physical activity and healthy diet, SGLT2 inhibitors</i> |
| CAD | <i>Lifestyle changes, statin therapy</i> |

Table 1-9: ESC Recommendations for the primary prevention of HF in patients with risk factors for its development:

| Recommendations | Class | Level |
|---|--------------|--------------|
| In order to prevent or delay the onset of HF: | | |
| ○ <i>Treatment of hypertension is recommended.</i> | I | A |
| ○ <i>Treatment with statins is recommended in patients at high risk of CV disease.</i> | I | A |
| ○ <i>SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease.</i> | I | A |
| ○ <i>Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended.</i> | I | C |

Follow-up of chronic heart failure:

ESC guidelines recommend follow-up at intervals no longer than 6 months to check symptoms, heart rate and rhythm, BP, full blood count, electrolytes, and renal function. For patients recently discharged from hospital, or in those undergoing uptitration of medication, follow-up intervals should be more frequent.

- An ECG should be done annually to detect QRS prolongation as such patients may become candidates for CRT. Furthermore, it may identify conduction disturbances and AF.
- Serial echocardiography is not necessary, although an echocardiogram should be repeated if there has been a deterioration in clinical status. An echocardiogram is also advised 3-6 months after optimization of standard therapies to determine the need for addition of newer drugs and implanted devices.
- Monitoring with biomarkers: They are undoubtedly good prognostic markers. However, current evidence does not support the routine measurement of BNP or NT-proBNP to guide titration of therapy.

Co-morbidities:

Importance of co-morbidities in patients with heart failure:

- Interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea)
- Aggravate HF symptoms and further impair quality of life.
- Contribute to the burden of hospitalizations and mortality.
- May affect the use of treatments for HF (e.g., beta-blockers relatively contraindicated in asthma).
- Evidence base for HF treatment is more limited as co-morbidities were mostly an exclusion criterion in trials, efficacy and safety of interventions is therefore often lacking in the presence of co-morbidities.
- Drugs used to treat co-morbidities may worsen HF (e.g. NSAIDs given for arthritis).
- Interaction between drugs used to treat HF and those used to treat co-morbidities.

▪ Chronic coronary syndrome:

- CAD is the most common cause of HF and should be considered as possible cause of HF in all patients presenting with new onset HF.
- Beta-blockers are the mainstay of therapy in patients with HFrEF and CAD because of their prognostic benefit. Ivabradine should be considered as an alternative to beta-blockers (when contraindicated) or as additional anti anginal therapy in patients in SR whose heart rate is ≥ 70 b.p.m.
- Other anti-anginal drugs (e.g., amlodipine, felodipine, nicorandil, ranolazine, and oral or transdermal nitrates) are indicated in case of persisting symptoms.
- Trimetazidine seems to have additive effects, such as improvement of LV function and exercise capacity, in patients with HFrEF and CCS already on beta-blockers.
- Diltiazem and verapamil increase HF-related events in patients with HFrEF and are contraindicated.

▪ **Atrial Fibrillation:**

- AF and HF frequently coexist. They can cause or exacerbate each other through mechanisms such as structural cardiac remodelling, activation of neurohormonal systems, and rate-related LV impairment.
- The detrimental effects of AF on LV function may be caused by an AF-related atrial myopathy or by tachycardic heart rates or by AF-related impaired systolic Ca^{2+} handling in LV cardiomyocytes.
- In contrast to the 'common belief', AF in HFrEF was not related to worse outcomes compared to SR either in chronic presentation or in acute decompensation of these patients. The independent association of AF with either HF hospitalizations by itself or combined with mortality remained significant only in patients with HFpEF and HFmrEF (ESC HF Long-Term Registry).
- Potential causes or precipitating factors (e.g, hyperthyroidism, MV disease) should be corrected.
- Worsening congestion due to AF should be managed with diuretics. Congestion relief may reduce sympathetic drive and ventricular rate and increase the chance of spontaneous return to SR.
- Long-term oral anticoagulant is recommended in all patients with HF and AF (regardless type of AF).
- Rhythm Control: There is insufficient evidence in favour of a strategy of rhythm control with antiarrhythmic drugs versus rate control in the patients with HF and AF.

Catheter ablation showed a consistent improvement in symptoms compared with medical therapy. However, the effects on mortality and hospitalization related to a small number of events and are insufficient to draw definitive conclusions.

- Rate Control: Lenient rate control is an acceptable initial approach. However, treatment targeting a lower heart rate may be needed if there are persistent symptoms or cardiac dysfunction related to tachycardia.
- AV node ablation can be considered in patients with poor ventricular rate control despite medical treatment not eligible for rhythm control by catheter ablation or in patients with biventricular pacing.

▪ **Valvular heart disease:** (For more details, See chapter 12)

▪ **Hypertension:**

- Treatment of HFrEF is similar in hypertensive and normotensive patients.
- Uncontrolled hypertension in patients with HFrEF is rare, provided the patient is receiving OMT at recommended doses for HF.
- Non-dihydropyridine CCBs (diltiazem and verapamil) and centrally acting agents (such as moxonidine) are contraindicated as they are associated with worse outcomes. Alpha-blockers have no effects on survival and are therefore not indicated.
- Hypertension is the most important cause of HFpEF. Patients with HFpEF also have an exaggerated hypertensive response to exercise and may present with hypertensive acute pulmonary oedema.
- Every effort should be made to reach target doses of evidence-based medications in HFrEF, despite slight hypotension. Conversely, in HFpEF with LVH and limited preload reserve, hypotension should be avoided.

▪ **Cancer:**

- HF occurs in patients with cancer as a result of the interaction among anti-cancer therapy, cancer itself, and patients' CV background (risk factors and coexisting CV disease).
- All patients scheduled for potential cardiotoxic therapies should undergo a baseline risk assessment using the **HFA-ICOS risk assessment** to evaluate the risk of receiving the cancer therapy and the intensity of monitoring during and after cancer treatment.

- History of HF or CMP and baseline LVEF < 50% characterize patients as being at very high risk or at high risk for all cancer therapies, except anti-androgen treatments for prostate cancer. Elevated levels of NPs or troponin at baseline are additional criteria of medium risk for most of the cancer treatments.
- ACE-I and a beta-blocker (preferably carvedilol) should be started in patients who develop LV systolic dysfunction, defined as $\geq 10\%$ absolute reduction in LVEF to a value below 50%.
- Global longitudinal strain (GLS) can detect cardiac dysfunction at an earlier stage. A $\geq 12\%$ relative reduction in GLS was compared with LVEF decline in high-risk patients undergoing cardiotoxic chemotherapy.
- Patients on immunotherapy with immune checkpoint inhibitors are at increased risk of myocarditis and should be monitored for related symptoms and signs and by weekly assessment of cardiac troponin during at least the first 6 weeks of therapy and managed accordingly.

▪ **Stroke:**

- A higher risk of stroke is present in HF patients in SR. AF confers an additional risk and patients with HF and AF have a five-fold increased risk compared to the control population.
- As a temporal trend, the incidence of stroke is higher in the first 30 days after HF diagnosis or an episode of HF decompensation and decreases in the first 6 months following the acute event.
- There are no data to support a routine anticoagulation in patients with HFrEF in sinus rhythm. However, low dose rivaroxaban may be considered in patients with concomitant CCS or peripheral artery disease, a high risk of stroke and no major hemorrhagic risk.
- Patients with visible intraventricular thrombus or at high thrombotic risk (such as those with history of peripheral embolism or PPCM or LV non-compaction) should be considered for anticoagulation.

▪ **Diabetes:**

- SGLT inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin or sotagliflozin) are recommended to prevent HF and CV death and worsening kidney function in patients with type 2 diabetes and CV disease and/or CV risk factors, or CKD.

- Metformin is thought to be safe in patients with HF, compared with insulin and sulfonylureas, based on observational studies. However, it is not recommended in patients with an eGFR < 30 mL/min/1.73 m² or hepatic impairment because of the risk of lactic acidosis.
- Sulfonylureas were associated with a higher risk of HF events and not a preferred treatment in patients with HF and patients should be monitored for evidence of worsening of HF after treatment initiation.
- Thiazolidinediones (glitazones) cause sodium and water retention and an increased risk of worsening HF and hospitalization. They are contraindicated in patients with HF.
- DPP-4 inhibitors and GLP-1 analogues are not recommended to reduce CV events in HF patients with DM.
- Insulin is needed in patients with type 1 diabetes and to control hyperglycaemia in some patients with type 2 diabetes, especially when beta-cell function is exhausted. It is a sodium-retaining hormone and concern has been raised that it may exacerbate fluid retention in patients with HF. However, in a RCT that included patients with type 2 diabetes, insulin did not increase the risk of incident HF. If insulin is needed in a patient with HF, the patient should be monitored for evidence of worsening of HF after treatment initiation.

▪ **Thyroid disorders:**

- Assessment of thyroid function is recommended in all patients with HF as both hypo- and hyperthyroidism may cause or precipitate HF.
- Subclinical hypothyroidism and isolated low T3 levels were associated with poorer outcomes in observational studies in patients with HF. There are no randomized trials evaluating the efficacy of thyroid replacement therapy in subclinical hypothyroidism, but there is a general agreement to correct it when the TSH is > 10 mIU/L, particularly in patients < 70 years.

▪ **Obesity:**

- Obesity is a risk factor for hypertension and CAD and is also associated with an increased risk of HF.
- Once obese patients have HF, an **obesity paradox** has been described such that overweight or mildly/moderately obese patients have a better prognosis than leaner patients, particularly compared with those who are underweight. However, other variables may influence this relationship and the obesity paradox is not observed in patients with diabetes.

- Proposed mechanisms of obesity paradox include: the earlier onset of HF in obese patients due to more severe symptoms, better tolerability of cardioprotective medications due to hypertension or the higher volume of distribution, the attenuated response of the RAAS system, less sarcopenia and cachexia, as well as implications for cardiorespiratory fitness.
- Of note, Obesity paradox was based on BMI measurements as an indicator for obesity. However, CV outcomes have stronger relationship with central/visceral obesity (more accurately assessed with waist-to-height ratio ⁽¹⁾) and skeletal muscle mass (assessed with dual-energy X-ray absorptiometry (DEXA)) than BMI.
- Caloric restriction and exercise training had additive beneficial effects on exercise capacity and QOL of patients with obesity and HFpEF.

▪ **Frailty, cachexia, sarcopenia:**

- **Frailty** is a multidimensional dynamic state, independent of age that makes the individual more vulnerable to the effect of stressors. The treatment of frailty in HF should be multifactorial and targeted to its main components and may include physical rehabilitation with exercise training, nutritional supplementation as well as an individualized approach to treating comorbidities.
- **Cachexia** is defined as a '*complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass*'. Its major clinical feature is a loss of > 5% oedema-free body weight during the previous 12 months. Cachexia is a generalized wasting process that may coexist with frailty and may occur in 5-15% of patients with HF, especially HFrEF. As it is associated with other chronic diseases (e.g cancer), alternative non-cardiac causes for cachexia should always be investigated.
- **Sarcopenia** is defined by the *presence of low muscle mass together with low muscle function, strength, or performance*. The most effective strategy for sarcopenia treatment is *resistance exercise training*, possibly combined with a protein intake of 1-1.5 g/kg/day.

▪ **Anaemia and Iron deficiency:**

- According to WHO criteria, anaemia is defined as Hb < 12 g/dL in women and < 13 g/dL in men.

(1) NICE guidelines highlighted the waist-to-height ratio as a powerful predictor for the development of CV disease than BMI. The guideline summarizes a healthy approach as 'Keep your waist to less than half of your height'.

- The WHO defines iron deficiency as a serum ferritin < 15 ng/mL. However, in patients with HF, iron deficiency is defined as either a serum ferritin concentration < 100 ng/mL (absolute iron deficiency) or 100-299 ng/mL with transferrin saturation (TSAT) < 20% (functional iron deficiency). Ferritin tissue expression and concentration in the peripheral blood is increased by inflammation and several disorders such as infection, cancer, and HF. Hence, higher cut-off values have been applied for the definition of iron deficiency in HF.
- Iron deficiency, which can be present independently of anaemia, is present in up to 55% of chronic HF patients and in up to 80% of those with AHF. It may be caused by increased loss, reduced intake or absorption (i.e. malnutrition, gut congestion) and/or impaired iron metabolism caused by the chronic inflammatory activation of HF, although the exact cause of iron deficiency in HF remains unknown.
- Iron deficiency impairs myocardial and musculoskeletal metabolism, even in the absence of anemia.
- Physiological studies suggest an equally deleterious effect of iron deficiency in HFpEF. When depleting cardiomyocytes of iron, mitochondrial function is reduced, and contraction is impaired, but interestingly cardiomyocyte relaxation is equally affected.
- Erythropoietin stimulating agents are not indicated for the treatment of anaemia in HF as Darbepoetin-alpha failed to reduce all-cause death or HF hospitalization and increased the risk of thromboembolic events. However, iron supplementation with i.v. ferric carboxymaltose is safe and improves symptoms, exercise capacity, and QOL of patients with HFrEF and iron deficiency.
- Oral iron therapy is not effective in iron repletion and did not improve exercise capacity in patients with HFrEF. It is not recommended for the treatment of iron deficiency in the patients with HF.

▪ **Kidney dysfunction:**

- CKD and HF frequently coexist. CKD may worsen CV function causing hypertension and vascular calcification. HF may worsen renal function, through the effects of neurohormonal and inflammatory activation, increased venous pressure and hypoperfusion. Oxidative stress and fibrosis likely play a major role as pathogenic mechanisms in HF with CKD.
- When RAAS inhibitors, ARNI or SGLT2 inhibitors are started, the initial decrease in the glomerular filtration pressure may decrease GFR and increase serum creatinine. However, these changes are generally transient and occur despite improvement in patient outcomes and slower worsening of renal function in the long term. An increase in serum creatinine of < 50% above

baseline, as long as it is < 3 mg/dL, or a decrease in eGFR of $< 10\%$ from baseline, as long as eGFR is > 25 mL/min/1.73 m², can be considered as acceptable. Also, with respect to diuretic therapy, small and transient rises in serum creatinine during treatment of acute HF are not associated with poorer outcomes when the patient is free of congestion.

- It is proven that Beta-blockers reduce mortality in HFrEF patients with eGFR > 30 mL/min/1.73 m², whereas limited evidence is available regarding patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²).
- The improvement in cardiac output after CRT or LVAD implantation may be associated with, at least, a transient improvement in renal function. The benefits of ICDs may be reduced in patients with severe renal dysfunction because of the competing risk of nonarrhythmic causes of death.

▪ **Electrolyte disorders:**

- **Hyponatraemia** is defined as a serum sodium concentration lower than 136 mmol/L. It is common in HF and may be present in up to 30% of patients admitted to hospital with HF. It reflects neurohormonal activation and is a powerful independent marker of poor outcomes in patients with acute or chronic HF.

Severe hyponatraemia may cause neurologic symptoms (seizures, delirium) due to cerebral oedema and may require immediate treatment with hypertonic saline with serum sodium increases by 1-2 mmol/L per hour, though less than 8 mmol/L in 24 h as a more rapid correction increases the risk of myelinolysis.

Intravenous treatment is not required when hyponatraemia is less severe, e.g. > 124 mmol/L, and in the absence of symptoms.

- Fluid restrictions to < 1 L/day may be indicated to achieve negative water balance and treat hyponatraemia.
- Tolvaptan, an orally active selective arginine vasopressin V₂ receptor antagonist, can be considered to increase serum sodium and diuresis in patients with persistent hyponatraemia and congestion. However, no effects on outcomes have been shown in RCTs.
- **Hypochloraemia** (< 96 mmol/L) is a powerful independent predictor of mortality in patients with acute and chronic HF. The carbonic anhydrase inhibitor (Acetazolamide) increases chloride reabsorption causing a greater bicarbonate and sodium excretion in the proximal tubule of the nephron. It can increase serum chloride levels and diuresis in patients with severe HF at risk of diuretic resistance.

- **Serum potassium levels** have a U-shaped relation with mortality with the lowest risk of death within a relatively narrow range of 4 to 5 mmol/L. Its treatment includes the use of RAAS inhibitors, potassium-sparing diuretics, and prescription of oral potassium supplements (i.e. potassium chloride tablets).

Potassium binders bind to potassium in the GIT reducing its absorption. They can be used for acute and chronic potassium lowering. They include: sodium polystyrene sulfonate, and the newer more tolerated two agents: patiromer sorbitex calcium and sodium zirconium cyclosilicate (SZC).

Sodium polystyrene sulfonate should not be used as a maintenance medication as it may cause severe GI side effects, including bowel necrosis.

Table 1-10: Management of chronic hyperkalaemia in HF patients:

In patients with chronic or recurrent hyperkalaemia on/not on maximal tolerated dose of RAAS inhibitors, an approved K⁺-lowering agent may be initiated as soon as K⁺ levels are confirmed > 5.0 mEq/L.

Maintain treatment unless alternative treatable aetiology is identified.

RAAS inhibitors should be optimized when K⁺ levels are < 5.0 mEq/L.

○ **In patients with K⁺ levels of 4.5-5.0 mEq/L:**

- RAAS inhibitor therapy can be initiated/up-titrated.
- If K⁺ levels rise above 5.0 mEq/L, initiate an approved K⁺-lowering agent.

○ **In patients with K⁺ levels of 5.0-6.5 mEq/L:**

- An approved K⁺-lowering agent should be initiated.
- If levels < 5.0 mEq/L are detected, up-titrate RAAS inhibitor.

○ **In patients with K⁺ levels of > 6.5 mEq/L:**

- It is recommended to discontinue/reduce RAAS inhibitor.

▪ **Lung disease:**

- Overall, COPD affects about 20% of patients with HF and has a major impact on symptoms and outcomes. Pulmonary function testing with spirometry is recommended as the first diagnostic tool. It should be performed in euvoaemic patients to avoid congestion-related obstructive pulmonary function patterns.
- Beta blockers can worsen pulmonary function in individual patients, but are not contraindicated in either COPD or asthma, as stated in the GOLD and GINA societies, respectively.

▪ **Sleep-disordered breathing:**

- Sleep-disordered breathing occurs in more than one third of patients with HF and is even more prevalent in patients with AHF. The most common types are: central sleep apnoea (CSA, similar to Cheyne-Stokes respiration), OSA, and a mixed pattern of the two. CSA and OSA have been shown to be associated with a worse prognosis in HF. OSA is associated with an increased risk of incident HF in men.
- Polysomnography is the gold standard test for sleep disorders.
- **CSA** is the most common form of sleep-disordered breathing in HFrEF. It is characterized by repetitive episodes of apnea and hyperventilation which occurs predominantly during non-REM sleep. Optimization of heart failure therapy is the mainstay in treatment. Implantable phrenic nerve stimulation can be considered for symptomatic relief. Positive pressure airway masks are contraindicated in those patients.
- **OSA:** OSA is characterized with 5 attacks or more of apnea or hypopnea. It can be managed with weight loss, positive airway pressure (using CPAP, BiPAP, or adaptive servoventilation) and mandibular advancement splints.

▪ **Gout and arthritis:**

- Hyperuricemia is a common finding in patients with CHF with a prevalence up to 50%. Hyperuricemia may be caused or aggravated by diuretic treatment. For every 1 mg/dL increase in serum uric acid levels the risk of all-cause mortality and of HF hospitalization increases by 4% and 28%, respectively.
- With respect to treatment of acute gout attacks, NSAIDs can worsen renal function and precipitate acute HF decompensation. Colchicine should be preferred as it is associated with less side effects.

- Both febuxostat and allopurinol reduce uric acid levels. However, allopurinol was associated with a lower all-cause and CV mortality, compared with febuxostat and is therefore recommended as the first-choice urate-lowering drug in HF patients with no contraindication.
- **Erectile dysfunction:**
 - Erectile dysfunction is a serious problem in HF patients due to its association with CV risk factors, comorbidities (e.g. diabetes), lifestyle (e.g. inactivity), and treatment (e.g. drugs).
 - Phosphodiesterase type 5 inhibitors are generally safe and effective in patients with compensated HF ⁽¹⁾.
- **Depression:** Depression affects 20% of patients with HF and is severe in half of them. There is still no consensus on the best therapy for HF patients with depression. Depressive symptoms may improve with selective serotonin reuptake inhibitors (SSRI). Tricyclic antidepressants should be avoided for the treatment of depression in HF as they may cause hypotension, worsening HF, and arrhythmias.
- **Infection:** Influenza vaccination is associated with a reduced risk of all-cause death in patients with HF in observational studies and retrospective analyses. Influenza and pneumococcal vaccination, as well as COVID-19 vaccination, should be considered in patients with HF.

Table 1-11: ESC Recommendations for the treatment of comorbidities associated with symptomatic HFrEF:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--------------------------------|--------------|--------------|
| Iron deficiency Anemia: | | |

(1) Nitrates should not be administered to patients within 24 h of sildenafil or vardenafil or within 48 h of tadalafil administration.

| | | |
|--|------------|----------|
| <i>It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.</i> | I | C |
| <i>Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose:</i> | | |
| <i>- is recommended in symptomatic patients with HFrEF and HFmrEF and iron deficiency ⁽¹⁾, to alleviate HF symptoms, improve exercise capacity and QOL.</i> | I | A |
| <i>- should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.</i> | Ila | B |
| Diabete and chronic kidney disease: | | |
| <i>SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.</i> | I | A |
| <i>SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.</i> | I | A |
| <i>In patients with T2DM and CKD, SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.</i> | I | A |
| <i>In patients with T2DM and CKD, finerenone is recommended to reduce the risk of HF hospitalization.</i> | I | A |
| Cancer: | | |
| <i>It is recommended that cancer patients at increased risk for cardiotoxicity, defined by a history or risk factors of CV disease, previous cardiotoxicity or exposure to cardiotoxic agents, undergo CV evaluation before scheduled anticancer therapy, preferably by a cardiologist with experience/interest in CardioOncology.</i> | I | C |

(1) Iron deficiency= serum ferritin < 100 ng/mL or serum ferritin 100-299 ng/mL with TSAT < 20%. TSAT= serum iron/TIBC.

| | | |
|---|------------|----------|
| <i>Treatment with an ACE-I and a beta-blocker (preferably carvedilol) should be considered in cancer patients developing LV systolic dysfunction, (defined as a 10% or more decrease in LVEF and to a value lower than 50%), during anthracycline chemotherapy.</i> | Ila | B |
| <i>A baseline CV risk assessment should be considered in all cancer patients scheduled to receive a cancer treatment with the potential to cause heart failure.</i> | Ila | C |

Heart failure with mildly reduced ejection fraction

- The diagnosis of HFmrEF requires the presence of symptoms and/or signs of HF, and a mildly reduced EF (41-49%). The presence of elevated NPs (BNP \geq 35 pg/mL or NT-proBNP \geq 125 pg/mL) and other evidence of structural heart disease [e.g., increased LA size, LVH or echocardiographic measures of LV filling] make the diagnosis more likely but are not mandatory for diagnosis.
- There is a substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodelling, and outcomes among the LVEF categories in HF. Patients with HFmrEF have features that are more similar to HFrEF than HFpEF. Also, Retrospective analyses from RCTs in HFrEF or HFpEF that have included patients with ejection fractions in the 40-50% range suggest that they may benefit from similar therapies to those with LVEF \leq 40%. This supports the renaming of HFmrEF from 'heart failure with mid-range ejection fraction' to 'heart failure with mildly reduced ejection fraction'.
- SGLT2is reduced CV death in individuals with HFmrEF/HFpEF. As in other forms of HF, diuretics should be used to control congestion. No substantial prospective RCT has been performed exclusively in patients with HFmrEF.

Table 1-12: ESC Recommendations for Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction:

| Recommendations | Class | Level |
|-----------------|-------|-------|
|-----------------|-------|-------|

| | | |
|--|------------|----------|
| <i>An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death ⁽¹⁾.</i> | I | A |
| <i>Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.</i> | I | C |
| <i>An ACE-I/ARB, beta-blocker, MRA and Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.</i> | IIb | C |

Heart failure with preserved ejection fraction

Pathophysiology: Cardiovascular pathophysiological processes include:

- increased systemic vascular resistance, increased conduit arterial stiffness, abnormal ventricular-arterial coupling, reduced LV long-axis systolic function, slowed early diastolic relaxation, reduced LV compliance with increased end diastolic stiffness, reduced LA reservoir and contractile function, impaired RV function, and chronotropic incompetence.
- Patients often have reduced reserve of stroke volume, heart rate, and cardiac output, and the increase in CO relative to oxygen consumption is blunted.
- Patients with HFpEF typically have high LV filling pressures, whether at rest and/or on exercise, and they may develop fluid retention and an expanded plasma volume.

▪ **Diagnosis:** If patient presented with dyspnea and/or edema with LVEF \geq 50%:

1. **Assess for non-cardiac source:** including renal failure or nephrotic syndrome, liver cirrhosis, anemia, severe obesity with peripheral edema, lung disease with or without cor pulmonale, and chronic respiratory failure hypoventilation syndrome. Thus, based on the clinical presentation, evaluation may include urinalysis to assess for proteinuria, abdominal ultrasound to assess for cirrhosis, and pulmonary evaluation with imaging, spirometry, and arterial blood gas.

(1) This recommendation is based on the reduction of the primary composite endpoint in EMPEROR-Preserved and DELIVER trials. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

2. **Apply universal definition of HF:** The Universal Definition of HF requires symptoms and/or signs of HF, caused by structural/functional cardiac abnormalities and at least 1 of the following: **1)** elevated natriuretic peptides; or **2)** objective evidence of cardiogenic pulmonary or systemic congestion.
3. **Assess for HF mimics:** History, physical examination and echocardiogram may suggest conditions such as RV failure, pulmonary hypertension, and valvular heart disease, or raise suspicion for other myocardial or pericardial diseases, requiring further workup. CMR may support the diagnosis of infiltrative or hypertrophic cardiomyopathy, or pericardial disease.
4. **Assess likelihood of HFpEF based on scoring systems (H2FPEF or HFA-PEFF scores):** Several diagnostic criteria have been proposed by HF societies and in clinical trials. These criteria vary widely in their sensitivities and specificities for diagnosing HFpEF. These scores include H2FPEF and HFA-PEFF scores.

H2FPEF score:

| Table 1-13: H2FPEF score: | | |
|--|--|----------|
| H2 | Heavy BMI > 30 kg/m ² | 2 |
| | On ≥ 2 antiHypertensive | 1 |
| F | Atrial Fibrillation | 3 |
| P | Pulmonary hypertension (PASP > 35 mmHg on Doppler echo) | 1 |
| E | Elderly (Age > 60 years) | 1 |
| F | LV Filling pressure (E/e' > 9 on Doppler echo) | 1 |
| ≥ 6 points = highly diagnostic of HFpEF 2-5 points = Intermediate probability 0-1 points = rule out | | |

N.B: The diagnosis of HFpEF in patients with AF is difficult.

Since AF is associated with higher NP levels, the use of NT-proBNP or BNP for diagnosing HFpEF probably needs to be stratified by the presence of sinus rhythm (with lower cut-offs) vs. AF (higher cut-offs).

LA Volume Index is increased by AF, and functional parameters of diastolic dysfunction are less well established in AF, and other cut-off values probably apply.

On the other hand, AF might be a sign of the presence of HFpEF, and patients with AF and HFpEF often have similar patient characteristics.

Table 1-14: Objective evidence of cardiac structural, functional and serological abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures:

| Parameter | Threshold | Comments |
|--|---|---|
| BNP | - > 35 (SR) or - > 105 (AF) pg/mL | <i>The main trigger for release of NPs is high LV end-diastolic wall stress, which is inversely proportional to wall thickness. So, up to 20% of patients with invasively proven HFpEF have NPs below diagnostic thresholds (or even normal) where LVH tends to normalize wall stress, particularly in the presence of obesity.</i> |
| NT-pro-BNP | - > 125 (SR) or - > 365 (AF) pg/mL | |
| Echocardiographic parameters: (Presence of structural alterations supports, but its absence does not exclude HFpEF) | | |
| LV mass index | - ≥ 95 g/m ² (Female) - ≥ 115 g/m ² (Male) | <i>Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LVH does not exclude the diagnosis of HFpEF ⁽¹⁾.</i> |
| Relative wall thickness | - RWT > 0.42 | |
| LA volume index | - > 34 mL/m ² (SR) - > 40 mL/m ² (AF) | <i>The maximal volume of the LA, measured at end-systole and indexed to BSA. In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure. In</i> |

(1) LV geometry is classified using RWT ($RWT = 2 \times \text{LV posterior wall thickness} / \text{LVIDD}$) and LVMI into 4 patterns:

Normal: normal LVMI, $RWT \leq 0.42$,

Concentric remodelling: Normal LVMI, $RWT > 0.42$,

Concentric hypertrophy: increased LVMI, $RWT > 0.42$,

Eccentric hypertrophy: increased LVMI, $RWT \leq 0.42$.

| | | |
|-----------------------------|-------------|---|
| | | <i>patients without AF or heart valve disease, LAVI > 34 mL/m² independently predicts death, HF, AF, and ischaemic stroke.</i> |
| E/e' ratio at rest | - > 9 | <i>E/e' ratio reflects the mPCWP. The mitral E/e' index correlates with LV stiffness and fibrosis. The E/e' index is little influenced by age or changes in volume but it is influenced by the severity of LVH.</i> |
| PA systolic pressure | - > 35 mmHg | <i>Elevated PASP and reduced RV function are important predictors of mortality in HFpEF. Elevated PASP is indirect marker of LV diastolic dysfunction.</i> |
| TR velocity at rest | - > 2.8 m/s | |

▪ **Treatment:**

1. Management of comorbidities:

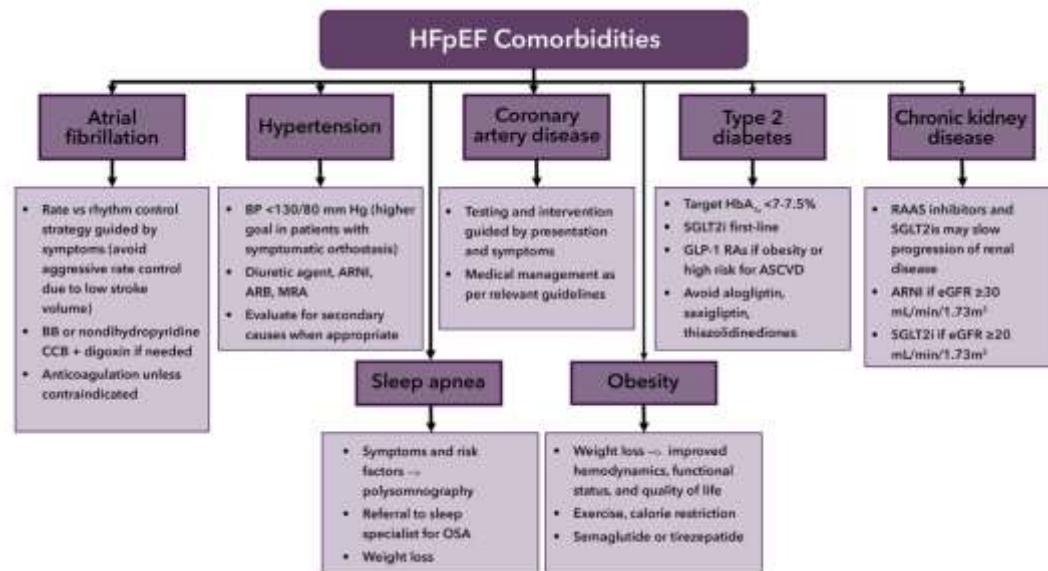


Figure 1-4: Management of Comorbidities associated with HFpEF. Source: Kittleson MM, Panjraht GS, Amancherla K, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2023 May 9;81(18):1835-78.

2. Non-pharmacological management, including:

- Exercise and weight loss: physical inactivity and obesity are strongly linked with poorer prognosis in HFpEF. Increased physical activity, preferably aerobic physical activity (e.g., brisk walking) for ≥ 150 min/week, is recommended for initial weight loss. Cardiac rehabilitation or structured exercise therapy could improve the quality of life and functional capacity, especially those with prior hospitalization.

- Implantable pulmonary artery pressure monitors (e.g., CardioMEMS): As volume management is a key therapeutic strategy in HFpEF, devices have been developed to monitor filling pressures and guide diuretic agent management (Class IIb in AHA/ACC/HFSA guidelines).

PA pressure monitoring may be most useful in the subset of individuals with HFpEF who: **1)** experience ≥ 1 hospitalization for HF and continue to experience NYHA class III symptoms despite GDMT; **2)** significant lability in volume status despite close ambulatory monitoring; **3)** have cardiorenal syndrome; or **4)** have comorbidities, such as obesity or chronic lung disease, for which differentiation of HF from other causes of dyspnea is difficult.

3. Pharmacological management:

- **SGLT2is:** all patients with HFpEF should be treated with SGLT2i to reduce CV death, HF hospitalization and improve health status.
- For Women (all LVEF spectrum) and Men with EF < 55-60% ⁽¹⁾:
 - **MRAs:** Although MRAs have not been shown to improve quality of life or exercise tolerance in HFpEF, MRAs are still beneficial to improve measures of diastolic function, provide balanced diuresis with sequential nephron blockade, control hypertension, and reduce HF hospitalizations ⁽²⁾.
 - **ARNI:** FDA granted sacubitril/valsartan an expanded HF indication, “to reduce the risk of CV death and hospitalization for HF in adult patients with chronic HF,” and noted that the “benefits are most clearly evident in patients with LVEF below normal” ⁽³⁾.

(1) The reason why women with HFpEF may respond more favorably to these therapies at a relatively higher EF may be because women tend to have smaller LV chamber size and are thus more prone to demonstrate higher LVEFs when compared with men.

(2) Subgroup in the TOPCAT study had a significant reduction in the primary endpoint of CV death and HF hospitalization, and a subsequent post hoc analysis by EF showed a significant reduction in outcomes for those with an LVEF < 55%.

(3) This decision was based on the subgroup analysis from the PARAGON-HF study, which showed a reduction in HF hospitalizations in those with an LVEF < 57%, and a meta-analysis of the PARADIGM-HF and PARAGON-HF studies, showing a reduction in CV death and HF hospitalization in those with an LVEF below the normal range.

- **ARB** may be used when ARNI is contraindicated (In CHARM-PRESERVED, candesartan reduced HF hospitalization. However, in I-PRESERVE, irbesartan did not reduce all-cause mortality or CV hospitalization).
- ACEIs are not considered a reasonable alternative (due to lack of benefit in the PEP-CHF trial).

| Table 1-15: ESC Recommendations for the treatment of patients with HFpEF: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF</i> | I | C |
| <i>An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death ⁽¹⁾.</i> | I | A |
| <i>Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.</i> | I | C |

Heart failure with improved ejection fraction (HFimpEF)

- **Definition:** patients with documented LVEF < 40% at baseline showing 10% or more absolute improvement in LVEF with the second measurement of LVEF > 40% (obtained at least after 3 to 6 months). These improvements in LVEF are typically accompanied by a reduction in LV volumes.
- **Why special category:**
 - Different characteristics: patients with HFimpEF have more favorable clinical, biomarker, and functional characteristics than those of HFrEF patients. However, HFimpEF patients as a group are distinct from healthy population.
 - Different clinical outcomes: patients with HFimpEF demonstrate significantly reduced rates of mortality and CV hospitalization compared to HFrEF and HFpEF patients. However, overall survival is still worse than in healthy population.

(1) This recommendation is based on the reduction of the primary composite endpoint in EMPEROR-Preserved and DELIVER trials. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

- **Pathophysiology:**

Reverse remodeling describes the biological process of restoration of more normal cardiac myocyte size and LV chamber geometry, resulting in a leftward shift of the pressure volume relationship toward normal. This process includes the following changes:

- Changes in myocyte biology: e.g., changes in gene expression that regulate different functional domains of the cell; including the sarcomere, β -adrenergic signaling, excitation contraction coupling, metabolism, and the cytoskeleton.
- Changes in extracellular matrix: restoration of ECM content and organization.

N.B: Accumulating evidence shows that the molecular changes associated with heart failure, in particular in the transcriptome, metabolome, and extracellular matrix, persist in the reverse-remodelled myocardium despite apparent normalization of macrolevel properties.

- **Frequency of recovery:** Frequency of LVEF improvement depends mainly on the cause of the underlying cardiomyopathy. The highest rates of recovery of LV function is associated with:

- Abnormal energetics: e.g., tachycardia-induced cardiomyopathy.
- DCM associated with inflammatory/immune responses, (e.g., peripartum cardiomyopathy, acute lymphocytic myocarditis).
- Toxin induced cardiomyopathy after discontinuation of cardiotoxins, (e.g., Alcohol and cancer chemotherapies).
- Stress-related cardiomyopathies: e.g., takotsubo cardiomyopathy.

- **Predictors of recovery:** the following parameters are more likely to have recovery:

- Clinical Parameters: Female gender, non-ischemic aetiology, shorter duration of HF, LBBB in CRT.
- Biomarkers: Lower troponin, greater reductions in NT-proBNP with HF therapy, Lower sST2 (inflammation), and lower Galectin-3 (fibrosis).
- Imaging Parameters: Lower EF with greater contractility on strain (GLS > 16), Smaller LV dimensions, No LGE on CMR.
- Genetic factors: e.g., activating mutation in the ACE or adrenergic receptor genes may attenuate LVEF response to medical therapy. Also, truncating mutations in the titin-A gene have higher frequency of LVEF improvement (except in patients with peripartum cardiomyopathy).

- **How to achieve recovery?**

- Removal of the causative agent: e.g., cessation of alcohol in alcoholic cardiomyopathy.
- Pharmacological therapy (GDMT) for HFrEF.
- Device therapy e.g LVAD and CRT.
- Specific interventions: e.g., restoration of sinus rhythm in patients with AF by catheter ablation, aortic valve replacement in patients with severe aortic stenosis.

- **How to maintain recovery ?**

Based on TRED-HF trial, it is recommended to continue HF therapies, including device therapies, in patients with HFimpEF even in patients with alcohol-induced cardiomyopathy to prevent deterioration.

- **Predictors of relapse:**

- Older age.
- The need for persistent diuretics.
- Presence of LBBB. In absence of a complete normalization of the ECG, it should be assumed that myocardial disease remains present.
- Echocardiographic predictors: Lower LVEF, Larger LV size, less negative GLS at the time of LVEF improvement increases the risk of future deterioration of LVEF.
- Discontinuation of HF medication.
- Lower glomerular filtration rate.

- **Follow up:** Follow up visits should be every 6 months for at least 3 years, then yearly.

Each visit should include: clinical evaluation, ECG, Echo with strain, NT-proBNP and CMR (after one year of clinically stable patients if not performed at de novo diagnosis of HFrEF).

Atrial Myopathy

- **Definition:**

Complex of subclinical structural, electrophysiological, and functional changes that affect the atria with the potential to produce clinical consequences.

It has been suggested that atrial disease links the pathophysiology of HF, especially HFpEF, with AF, as they often coexist, are closely inter-related and share common risk factors.

- **Pathophysiology:**

- **Stage A:** Fibroblast proliferation and extracellular matrix deposition in response to insults such as aging, inflammation, oxidative stress, and atrial stretch from volume and/or pressure overload. At this stage, clinical atrial myopathy is not detectable.
- **Stage B:** Besides structural changes, electrophysiological remodeling (including alterations in calcium cycling, ion channels, and gap junctions) starts to occur. In this stage, atrial myopathy is established and becomes detectable, but the individual remains asymptomatic.
- **Stage C:** ongoing inflammation and remodeling cause endothelial activation contributing to the development of a pro-inflammatory and pro-thrombotic environment. In this stage, the myopathic atria become manifest in the form of AF and stroke. AF leads to a pro-thrombotic state that feeds back to cause more atrial fibrosis and inflammation facilitating more AF.
- At stage C, the manifest atrial myopathy can be reversed by aggressive interventions such as lifestyle modification and successful AF ablation. If failure to reverse occurs, the disease progresses to **stage D**, or end-stage atrial myopathy.

- **Diagnosis:**

- Non-AF atrial arrhythmias (e.g., frequent PACs or paroxysmal atrial tachycardia) might indicate an abnormal atrial substrate and a predisposition to AF, and have been associated with increased risk of stroke in long-term follow-up, independent of diagnosed AF.
- Imaging can be a useful tool in detecting patients with atrial myopathy.
 - Echocardiography (2D echocardiography, pulsed-wave Doppler, and strain imaging) is useful in providing LA volumetric and functional assessment.

- CMR LGE has been applied to assess the extent of LA fibrosis and was found to be an independent risk factor of stroke and correlated with AF recurrence after catheter ablation. Also, (4D) flow CMR provides a comprehensive characterization of atrial flow dynamics deriving stasis maps that provide visualizations and quantification of stasis in LA and LAA, the typical site of thrombus formation.
- Cardiac biomarkers, including hs-troponins and NPs, may assess pathophysiological aspects of atrial disease. The increased levels of NPs in AF may also be an indicator of an underlying atrial disease.
- **Management:**
 - Effective management of HF, AF and mitral regurgitation may be important to counteract atrial disease progression.
 - The concept of atrial myopathy may help guide OAC deescalation in selected groups of patients with AF, particularly those who have undergone a successful AF ablation. Prospective randomized trials are needed to test these hypotheses.

Heart Failure in Pregnancy

Pregnancy in pre-existing heart failure

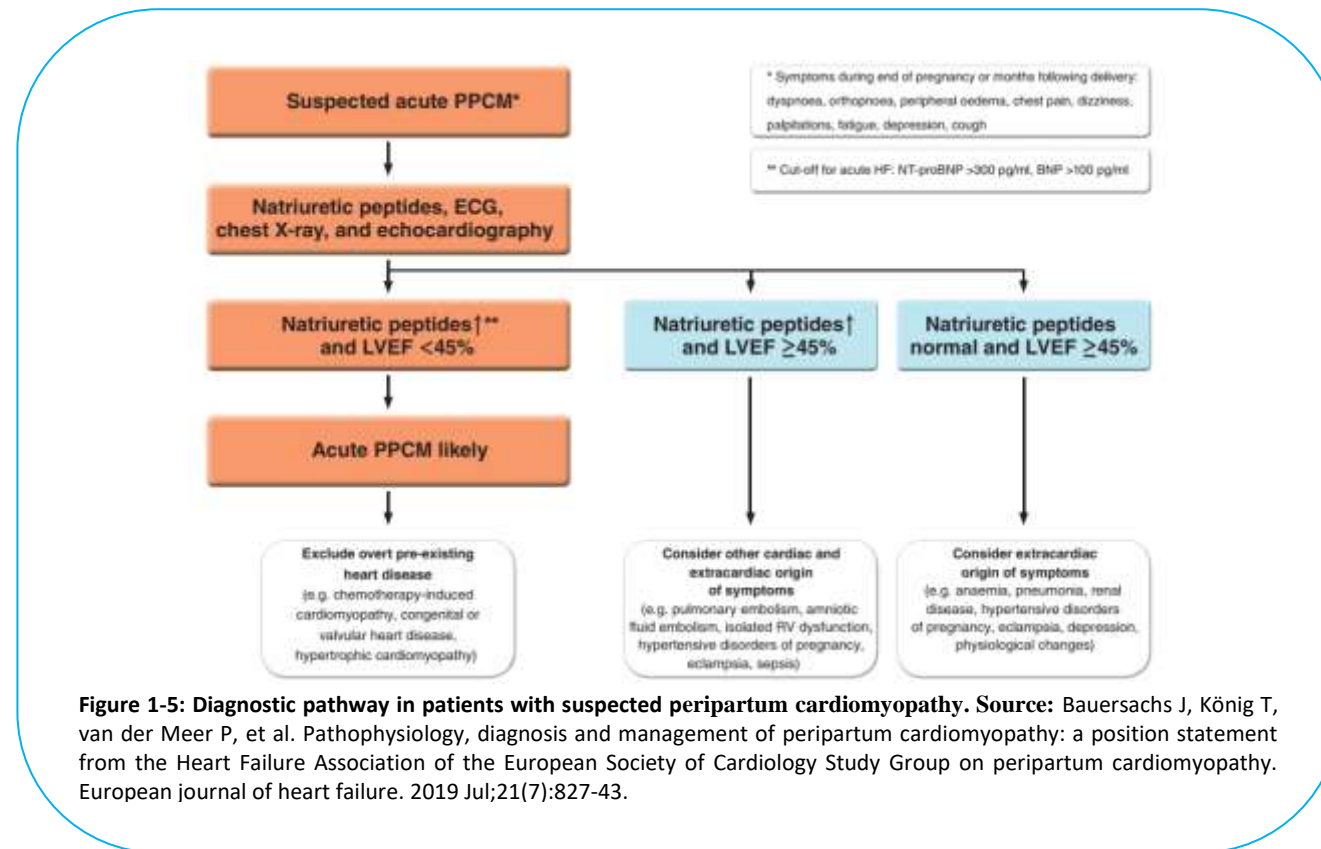
- Women with pre-existing HF have higher risk of CV complications including HF decompensation.
- Pre-pregnancy management includes the modification of existing HF medications to avoid foetal harm. ACE-Is, ARBs, ARNI, MRAs, ivabradine, and SGLT2 inhibitors should be stopped prior to conception.
Beta-blockers should be continued and switched to β 1-selective blockers (bisoprolol, metoprolol).
Hydralazine, oral nitrates and methyldopa can be started if required.
- In patients with HF and AF, therapeutic anticoagulation with LMWH, in the first and last trimesters. VKAs, with the usual target INR or LMWH for the second trimester. DOACs should be avoided.
- **Follow up:**
 - For women in mWHO II-III: Bimonthly assessments.
 - For women with pre-existing HF in mWHO III: monthly assessments.

- For women with advanced HF (LVEF < 30%, NYHA class III-IV) in mWHO IV: refer to a specialist centre for counselling regarding termination of pregnancy.
- **Mode of delivery:** should be planned by cardiologists, obstetricians, and anaesthesiologists around 35 weeks in a multidisciplinary Pregnancy Heart Team.

Peripartum cardiomyopathy (PPCM)

- **Definition:**
PPCM is idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction usually shown by an LVEF < 45%, occurring in the last month of pregnancy or in the months following delivery, without any other identifiable cause (It is a diagnosis of exclusion).
- **Predisposing factors:** Hypertension, multiparity and multiple pregnancies, family history, ethnicity, smoking, diabetes, pre-eclampsia, malnutrition, age of mother (with older mothers being at greater risk), and prolonged use of tocolytic beta-agonists.
- **Pathophysiology:**
 - The precise mechanism is ill-defined, but the 'two-hit' model is thought to be crucial in the pathophysiology of PPCM including:
 - (1) Inflammation and angiogenic imbalance, inducing vascular damage. Oxidative stress during pregnancy appears to be a trigger that activates cathepsin D in cardiomyocytes which cleaves prolactin into an angiostatic and pro-apoptotic subfragment that in turn leads to impaired endothelial function and cardiomyocyte metabolism.
 - (2) Host susceptibility (due to some baseline altered endothelial function).
 - Genetic role: it is thought that 15-20% of patients with PPCM carry mutations known to induce cardiomyopathies, i.e. in genes like titin, beta-myosin heavy chain, MYBPC3, lamin A/C or SCN5A.
- **Diagnosis:**
 - Clinical presentation:

- Early signs and symptoms of PPCM may often mimic normal physiological findings of pregnancy and include pedal oedema, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, and persistent cough. In the majority of patients, symptoms develop in the first 4 months after delivery (78%). Thus, *PPCM should be suspected in all women with a delayed return to the pre-pregnancy state.*
- Patients frequently present with acute HF, ventricular arrhythmias and/or cardiac arrest.
- Echocardiography is indicated in all cases of suspected PPCM to confirm the diagnosis, assess concomitant or pre-existing cardiac disease, exclude complications of PPCM (e.g. LV thrombus) and obtain prognostic information. Initial LVEF < 30%, marked LV dilatation (LV end-diastolic diameter \geq 6.0 cm), and RV involvement are associated with adverse outcomes. Echocardiography should be repeated before patient discharge and at 6 weeks, 6 months, and annually.
- CMR may provide a more accurate evaluation of cardiac structure and function, and can sometimes be helpful if there is high suspicion for another diagnosis such as ARVC and myocarditis. Administration of gadolinium to assess late enhancement should be avoided until after delivery due to the increased risk of stillbirth, neonatal death, and rheumatological, inflammatory, or infiltrative skin conditions.



- **Treatment:**

- Urgent delivery by cesarean section (irrespective of gestation) should be considered in women with advanced heart failure and haemodynamic instability despite optimal heart failure treatment.

- **Drug therapy:**

- During pregnancy:

ACEIs, ARBs, ARNI, MRAs and ivabradine are contraindicated because of concerns of teratogenicity and foetal toxicity. Hydralazine and nitrates can be used instead.

Beta-blockers are indicated in stable condition, with metoprolol succinate being the preferred agent.

Diuretics should be administered with caution as they may impair perfusion of the placenta.

- After delivery:

ACEIs can be started, with captopril or enalapril preferred during breastfeeding.

MRAs should be avoided during lactation, but should be started afterwards in stable patients.

Consider the prolactin blocker bromocriptine (2.5 mg twice daily for 2 weeks, followed by 2.5 mg per day for 6 weeks) in addition to standard HF therapy to reduce the production of a cleaved 16 kDa prolactin fragment ⁽¹⁾. If bromocriptine is not available, cabergoline may be used as an alternative.

- Since PPCM is associated with a high thromboembolic risk, oral anticoagulation is recommended in all patients with acute PPCM and LVEF $\leq 35\%$ or treated with bromocriptine (if no contraindication exists).
- If PPCM recovers, heart failure medication should be continued for at least 12-24 months after complete recovery of LV dimensions and systolic function.
- o **ICD:** Since this risk of sudden death is only transient in patients who eventually recover, a wearable defibrillator rather than an ICD may be justified. ICD is indicated in patients who do not recover their LV function within 6 months of medical therapy.
- o **In PPCM with cardiogenic shock:**
- Inotropes: Catecholamines should be avoided whenever possible or used only with extreme caution. Levosimendan, in contrast to dobutamine and adrenaline, does not increase myocardial oxygen demand and may be considered as the preferred inotrope. Noradrenaline should be the first-line vasopressor.
- Mechanical Circulatory Support (MCS): (e.g., ECMO) should be considered early as a rescue therapy in patients who cannot be stabilized with medical therapy alone. After the initial phase, if no weaning from mechanical circulatory support can be achieved after a maximum of 7-10 days, a switch to a durable device (e.g LVAD) should be planned.

(1) *Effective suppression of prolactin with high bromocriptine doses up to 10 mg B.I.D under sequential measurements of prolactin level may be used in PPCM patients supported with ECMO as increased prolactin levels during ECMO have been reported.*

- Heart transplant is reserved for patients where MCS is not possible or satisfactory ventricular recovery after 6-12 months is not achieved. Post-transplant outcomes in women with PPCM appear to be worse than in other recipients.
- **Prognosis and counseling:**
 - Cardiac recovery may occur in the first 3-6 months though it may be delayed to up to 2 years. Recovery rates vary among regions, from 75% to less than 50%.
 - 6-month visit including echocardiography is recommended in all women until they recover to an LVEF > 50%. In women with LV recovery who remain stable after tapering of heart failure drug therapy, an annual visit is recommended for up to 10 years.
 - Decisions on whether to terminate or continue breastfeeding with caution should be taken jointly with the patient on a case-by-case basis. In patients with severe heart failure, preventing lactation may be considered due to the high metabolic demands of lactation and breastfeeding.
 - Subsequent pregnancies should be avoided in patients with PPCM, even in those who recover their LV function. Contraception using Intrauterine devices (copper and progestogen-releasing IUDs) do not increase the risk of thromboembolism. Combined hormonal contraceptives should be avoided.

Advanced heart failure

- **Definition:** All the following criteria must be present despite optimal medical treatment:
 1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
 2. Severe cardiac dysfunction defined by at least one of the following:
 - LVEF \leq 30%.
 - Isolated RV failure (e.g., ARVC).
 - Non-operable severe valve abnormalities.
 - Non-operable severe congenital abnormalities.
 - Persistently high (or increasing) BNP or NT-proBNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF).

3. Episodes of: **(A)** Pulmonary or systemic congestion requiring high-dose i.v. diuretics (or diuretic combinations) or **(B)** Low output requiring inotropes or vasoactive drugs or **(C)** Malignant arrhythmias causing > 1 unplanned visit or hospitalization in the last 12 months.
 4. Severe impairment of exercise capacity (due to cardiac condition) with inability to exercise or 6MWT distance < 300m or CPET showing peak oxygen consumption < 12mL/kg/min or < 50% predicted value ⁽¹⁾.
- **Referral to HF specialized unit:**

| Table 1-16: 'I Need Help' markers to trigger referral to advanced heart failure unit: | | |
|---|-----------------------------------|---|
| I | <i>Inotropes</i> | <i>Previous or ongoing requirement for inotropic support</i> |
| N | <i>NYHA class/NP</i> | <i>Persisting NYHA class III or IV and/or persistently high BNP or NT-proBNP</i> |
| E | <i>End-Organ Dysfunction</i> | <i>Worsening renal or liver dysfunction in the setting of HF</i> |
| E | <i>Ejection Fraction</i> | <i>Very low EF < 20%</i> |
| D | <i>Defibrillator shocks</i> | <i>Recurrent appropriate defibrillator shocks</i> |
| H | <i>Hospitalizations</i> | <i>More than 1 hospitalization with HF in the last 12 months</i> |
| E | <i>Edema/Escalating diuretics</i> | <i>Persisting fluid overload and/or increasing diuretic requirement</i> |
| L | <i>Low blood pressure</i> | <i>Consistently low blood pressure with SBP < 90 to 100 mmHg</i> |
| P | <i>Prognostic medication</i> | <i>Inability to uptitrate (or need to decrease/cease) ACE-Is, beta-blockers, ARNIs, or MRAs</i> |

- **INTERMACS profiles:**

(1) 6MWT does not accurately reflect functional capacity as assessed by pVO₂, but it is correlated to pVO₂ and predicts survival in heart failure. Use of the 6MWT is encouraged to give objective evidence of functional impairment in patients with advanced heart failure where CPET is not indicated. In addition, the 6MWT can be a useful tool to assess frailty, which represents a significant risk marker and potential contraindication to non-pharmacologic strategies in advanced heart failure.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, developed to classify patients with a potential indication for durable MCS devices, describes clinical parameters and characteristics consistent with a need for advanced therapies. This classification has also been shown to be useful in estimating the prognosis of patients undergoing urgent heart transplantation or LVAD implantation, and for risk assessment in ambulatory advanced HF patients. Prognostic stratification is important to identify the ideal time for referral to an appropriate centre (i.e. one capable of providing advanced HF therapies), to properly convey expectations to patients and families, and to plan treatment and follow-up strategies.

Table 1-17: INTERMACS profile descriptions of patients with advanced heart failure

| Profile | Time frame for intervention |
|--|--|
| Profile 1. Critical cardiogenic shock: Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. “Crash and burn.” | Definitive intervention needed within hours. |
| Profile 2. Progressive decline: Patient with declining function despite i.v. inotropic support, may be manifest by worsening renal function, nutritional depletion, and inability to restore volume balance. “Sliding on inotropes.” | Definitive intervention needed within few days. |
| Profile 3. Stable on inotrope or inotrope-dependent: Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous i.v. inotropic support (or a temporary circulatory support or both) but demonstrating repeated failure to wean from support due to symptomatic hypotension or renal dysfunction. “Dependent stability.” | Definitive intervention elective over a period of weeks to few months. |
| Profile 4. Frequent Flyer: | |

| | |
|--|--|
| Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. | |
| Profile 5. Housebound: Comfortable at rest and with activities of daily living but unable to engage in any other activity, living predominantly within the house. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4, and require definitive intervention. | Variable urgency, depends upon maintenance of nutrition, organ function, and activity. |
| Profile 6. Exertion limited: Patient without evidence of fluid overload, comfortable at rest and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. "Walking wounded." | |
| Profile 7. Advanced NYHA class III symptoms: Patient without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion. | Heart transplantation or MCS may not be currently indicated. |
| Modifiers for profiles | Possible profiles that can be modified |
| Temporary MCS can modify profile only in hospitalized patients. This includes IABP, ECMO, TandemHeart, LVAD, Impella. | 1, 2, 3 in hospital |
| Arrhythmia can modify any profile. This includes recurrent VTs that have recently contributed to clinical compromise, frequent ICD shocks or requirement for external defibrillation, usually more than twice weekly. | 1-7 |

| | |
|--|--|
| Frequent episodes of HF decompensation requiring frequent emergency visits/hospitalizations for diuretics, ultrafiltration, or temporary vasoactive therapy. Frequent episodes may be considered as at least 2 emergency visits/admissions in the past 3 months or three in the past 6 months. | 3 if at home, 4, 5, 6. Rarely for profile 7 |
|--|--|

- **Management:**

- Inotropes may improve haemodynamic parameters, reducing congestion, augmenting cardiac output, and aiding peripheral perfusion. However, traditional inotropes may favor myocardial ischaemia and/or tachyarrhythmias and worsen the clinical course. Intermittent use of inodilators for long-term symptomatic improvement or palliation has gained popularity, especially use of levosimendan, since the haemodynamic effect may last for > 7 days after a 12-24 h infusion because of the pharmacologically active metabolite with a long half-life.
- Kidney dysfunction and loop diuretic resistance often characterize the clinical course of patients with advanced HF. Doubling of the loop diuretic dose is proposed, in the first instance, followed by concomitant administration of thiazides or metolazone. In patients who fail to respond to diuretic-based strategies, ultrafiltration or renal replacement therapies should be considered.
- Short-term MCS devices are indicated to reverse critical endorgan hypoperfusion and hypoxia in the setting of cardiogenic shock. The aim is to support the central nervous system and organ perfusion, to reverse acidosis and multi-organ failure until the patient's outcome becomes clearer be that of cardiac recovery, transition to durable MCS or heart transplantation, or, in some cases, towards a more palliative approach.
Short-term MCS should be used in patients with INTERMACS profiles 1 or 2 as a bridge to decision, bridge to recovery, bridge to bridge for either long-term MCS or urgent heart transplantation.
- When medical therapy is insufficient or when short term MCS has not led to cardiac recovery or clinical improvement, long term MCS can be considered as bridge to transplantation or to reverse contraindications to heart transplantation (bridge to candidacy) or as destination therapy.

Table 1-18: ESC Recommendations for the treatment of patients with advanced heart failure:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy and who do not have absolute contraindications.</i> | I | C |
| <i>Patients being considered for long-term MCS must have good compliance, appropriate capacity for device handling and psychosocial support.</i> | I | C |
| <i>Long-term MCS should be considered in patients with advanced HFrEF despite optimal medical and device therapy:</i> | | |
| - <i>If not eligible for heart transplantation or other surgical options, and without severe RV dysfunction, to reduce the risk of death and improve symptoms.</i> | IIa | A |
| - <i>As a bridge to cardiac transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death.</i> | IIa | B |
| <i>Renal replacement therapy should be considered in patients with refractory volume overload and end-stage kidney failure.</i> | IIa | C |
| <i>Continuous inotropes and/or vasopressors may be considered in patients with low cardiac output and evidence of organ hypoperfusion as bridge to MCS or heart transplantation.</i> | IIb | C |
| <i>Ultrafiltration may be considered in refractory volume overload unresponsive to diuretic treatment.</i> | IIb | C |

- **End-of-life care:**

- Patients with heart failure in whom end-of-life care should be considered:
 - Progressive functional decline (physical and mental) and dependence in activities of daily living.
 - Severe heart failure symptoms with poor QOL despite optimal medical and device therapy.
 - Frequent admissions to hospital or serious episodes of decompensation despite optimal treatment.
 - Heart transplantation and MCS ruled out.

- Cardiac cachexia.
- Clinically judged to be close to end of life.
- Treatment for symptoms needs to be considered. It may include additional intervention on top of OMT:
 - Breathlessness: repeat doses of opioids may be considered for the relief of dyspnoea; however, their effectiveness is not demonstrated. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. Increasing the inspired oxygen concentration may provide relief of dyspnoea.
 - Pain: non-pharmacologic management can be helpful. In addition, opioid, oxycodone, hydromorphone, and fentanyl are generally viewed as safe options.
 - Anxiety and depression: adequate conventional treatment should be offered.
- Advanced care planning, taking into account preferences for place of death and resuscitation (which may include deactivating devices, such ICD or long-term MCS) that require a multidisciplinary decision.

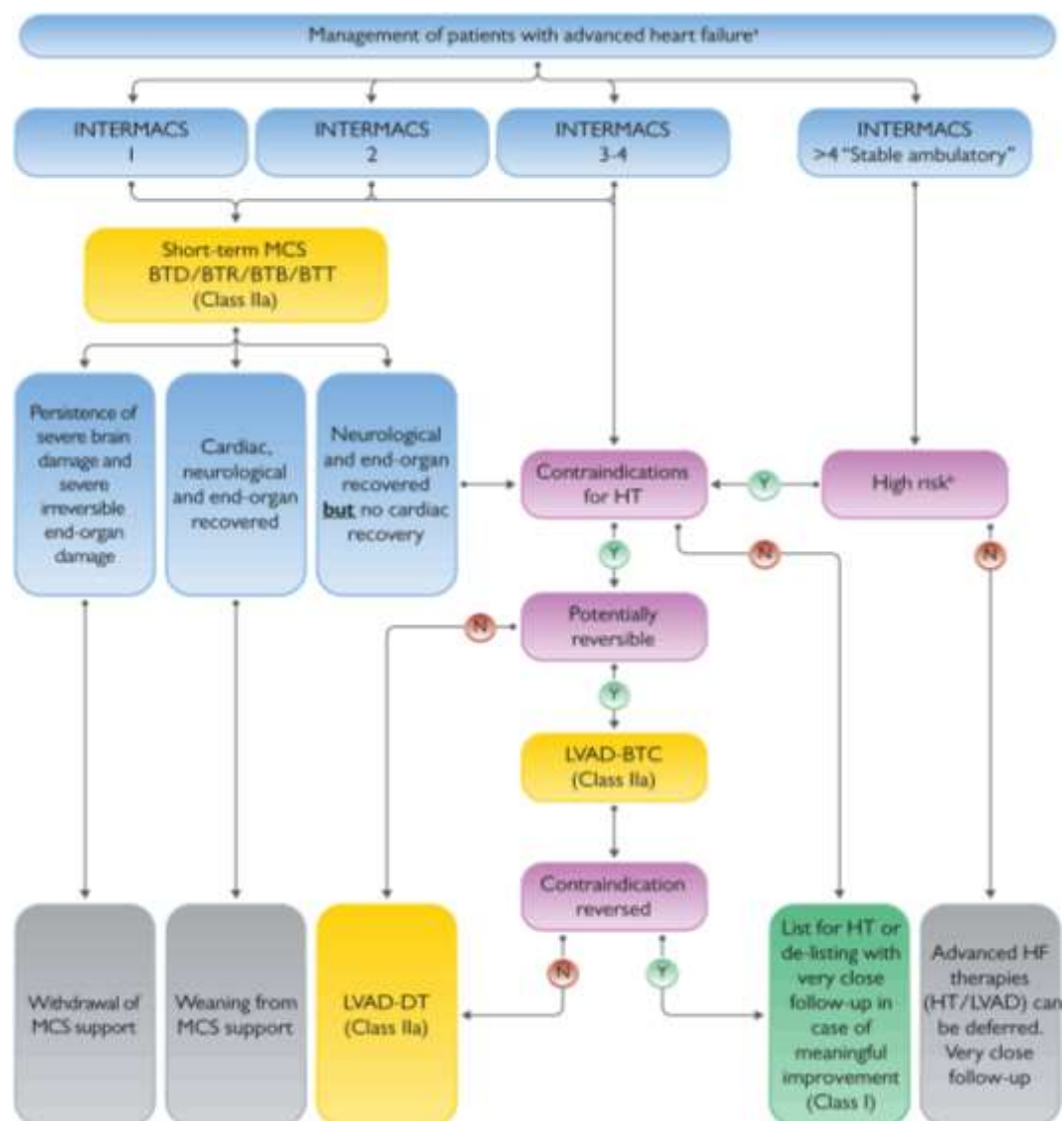


Figure 1-6: Algorithm for the treatment of patients with advanced heart failure. A) This algorithm can be applied to all patients with advanced HF, with exception of HCM, cardiac arrest, arrhythmic storm, adult congenital heart disease, refractory angina. **B)** Recurrent hospitalization, progressive end-organ failure, refractory congestion, inability to perform cardiopulmonary exercise test or peak oxygen consumption < 12 mL/min/kg or <50% of expected value. Colour code for classes of recommendation: Green for Class of recommendation I and Yellow for Class of recommendation IIa. **Source:** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

Important trials in Heart failure:

| Table 1-19: Clinical trials of HFrEF: | |
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| Trial (date) | Summary |
| ACEIs: | |
| CONSENSUS (1987) | <p>Aim: To evaluate the effect of the Enalapril on the prognosis of severe congestive heart failure (NYHA class IV)</p> <p>Study: 253 patients with LVEF $\leq 35\%$; NYHA I-IV; creatinine $< 177 \mu\text{mol/L}$ were randomly assigned to receive either enalapril or placebo. Conventional treatment for HF, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days. The primary end point was crude mortality at the end of six months. Enalapril improves survival in NYHA class IV HFrEF when added to standard therapy.</p> |
| SOLVD (1991) | <p>Aim: To evaluate the effect of Enalapril on mortality and hospitalization in patients with chronic heart failure and EF $\leq 35\%$</p> <p>Study: 2569 patients with chronic HF (LVEF $\leq 35\%$) were randomly assigned to receive either enalapril (2.5 to 20 mg) or placebo. Approximately 90% of the patients were in NYHA II and III. The follow-up averaged 41.4 months. Enalapril reduced 4-year mortality by 16% and reduced HF hospitalizations when added to conventional therapy in patients with HFrEF.</p> |
| TRACE (1995) | <p>Aim: To determine whether patients who have LV dysfunction soon after MI benefit from long-term ACEIs.</p> <p>Study: 1749 patients with MI were randomly assigned to receive oral trandolapril or placebo on days 3 to 7 after MI. The duration of follow-up was 24 to 50 months. Long-term treatment with trandolapril in patients with reduced LV function soon after MI significantly reduced the risk of overall mortality, CV mortality, sudden death, and the development of severe HF.</p> |
| ATLAS (1999) | <p>Aim: To evaluate if low and high doses of ACEIs have similar benefits to reduce morbidity and mortality in patients with heart failure.</p> |

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| | <p>Study: 3164 patients with LVEF $\leq 30\%$ in NYHA II-IV CHF were randomized to low doses (2.5-5.0 mg daily) or high doses (32.5-35 mg daily) of lisinopril and followed up for a median of 46 months. High dose of lisinopril causes a 10% reduction in CV mortality, and 15% reduction in combined all-cause mortality or HF hospitalization rate.</p> |
| ARBs: | |
| ValHeFT (2001) | <p>Aim: To evaluate the long-term effects of the addition of valsartan to standard therapy for heart failure.</p> <p>Study: 5010 patients with LVEF $< 40\%$, NYHA class II-IV, on ACE-I, LVDD > 2.9 cm/BSA were randomly assigned to receive valsartan (160 mg) or placebo twice daily. In a time when HFrEF therapy included ACEIs but not beta blockers, addition of valsartan to standard HFrEF therapy did not improve survival but reduced the incidence of the composite endpoint of morbidity and mortality, largely through a decrease in HF hospitalizations.</p> |
| VALIANT (2003) | <p>Aim: To test the hypothesis that treatment with valsartan alone or in combination with captopril would result in better survival after AMI than ACEI.</p> <p>Study: 14703 patients receiving conventional therapy were randomly assigned, 0.5 to 10 days after AMI, to additional therapy with valsartan alone, valsartan plus captopril, or captopril. The primary end point was death from any cause. Valsartan was as effective as captopril in improving survival among patients with HF and/or LV dysfunction in the post-MI period.</p> |
| CHARM-Added and Alternative (2004) | <p>Aim: To test the hypothesis that the morbidity and mortality of heart failure would be favorably affected by ARB therapy.</p> <p>Study: 4576 patients with CHF NYHA class II-IV with LVEF of $\leq 40\%$ were randomized to candesartan or placebo in 2 complementary parallel trials (CHARM-Alternative for patients who cannot tolerate ACEIs, and CHARM-Added for patients who were receiving ACEIs). Candesartan significantly reduces CV death and HF hospitalizations by 15% when added to ACEIs (CHARM-Added) and by 23% when intolerant to ACEI (CHARM-Alternative).</p> |
| ARNI: | |
| PARADIGM-HF | <p>Aim: To assess the long-term effects of sacubitril-valsartan on morbidity and mortality in patients with chronic HFrEF.</p> |

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| (2014) | <p>Study: 8442 patients with $EF \leq 40\%$ in NYHA class II-IV and $BNP \geq 150$ pg/mL or NT proBNP ≥ 600 pg/mL, (<u>or</u> $BNP \geq 100$ pg/mL or NT-proBNP ≥ 400 pg/mL if HF hospitalization within recent 12 months) were randomly assigned to receive either Sacubitril-valsartan (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of CV death or HF hospitalization. Among patients with HFrEF, ARNI reduced all-cause mortality by 16%, CV mortality by 20% and HF hospitalizations by 21% when compared to enalapril.</p> |
| EVALUATE-HF (2019) | <p>Aim: To determine whether sacubitril-valsartan improves central aortic stiffness and cardiac remodeling in HFrEF compared with enalapril.</p> <p>Study: 464 participants with heart failure and $LVEF \leq 40\%$ were randomly assigned to receive either sacubitril-valsartan or enalapril for 12 weeks. Sacubitril-valsartan, compared with enalapril, did not significantly reduce central aortic stiffness.</p> |
| PARADISE-MI (2021) | <p>Aim: to assess the efficacy and safety of sacubitril/valsartan compared with ramipril in acute MI population.</p> <p>Study: 5669 patients with AMI were randomly assigned to either sacubitril/valsartan (target dose 97/103 mg BID) or ramipril (target dose 5 mg BID). Sacubitril/valsartan did not reduce the primary endpoint (CV mortality and HF hospitalization) in AMI population, compared with ramipril.</p> |
| LIFE (2021) | <p>Aim: To assess the efficacy, safety, and tolerability of sacubitril/valsartan in patients with advanced chronic heart failure.</p> <p>Study: 335 patients with advanced heart failure were randomized to either sacubitril/valsartan (24/26 mg or 49/51 mg BID, uptitrated to 97/103 mg BID if tolerated after 4 weeks), or valsartan (40 or 80 mg BID, uptitrated to 160 mg BID if tolerated). Sacubitril/valsartan did not reduce NT-proBNP or clinical outcomes among patients with advanced HFrEF.</p> |
| Mineralocorticoid Receptor Antagonists: | |
| RALES (1999) | <p>Aim: to determine if spironolactone would significantly reduce the risk of all-cause mortality among patients who had severe heart failure.</p> |

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| | <p>Study: 1663 patients with HF for > 6 weeks and LVEF ≤ 35% in NYHA III-IV with creatinine ≤ 221 μmol/L (who were being treated with ACEIs, loop diuretic, and digoxin) were randomly assigned to receive spironolactone (25 mg), or placebo. Spironolactone reduced all-cause mortality by 30%.</p> |
| EPHESUS (2003) | <p>Aim: To evaluate the effect of eplerenone on morbidity and mortality among patients with AMI complicated by LV dysfunction and heart failure</p> <p>Study: 6632 patients with AMI complicated by HF and systolic LV dysfunction were randomly assigned to eplerenone or placebo in addition to optimal medical therapy. The primary end points were death from any cause and CV death or HF hospitalization, AMI, stroke, or ventricular arrhythmia. Eplerenone reduced the rate of mortality among patients with acute MI complicated by LV dysfunction and HF symptoms.</p> |
| EMPHASIS-HF (2011) | <p>Aim: To investigate the effects of eplerenone, added to evidence-based therapy, on clinical outcomes in patients with systolic HF and mild symptoms</p> <p>Study: 2737 patients with NYHA class II, heart failure and EF < 30% (or LVEF 30-35% with QRS > 130 ms), CV hospitalization in recent 6 months <u>or</u> BNP ≥ 250 pg/mL or NT proBNP ≥ 500 pg/mL in men (and ≥ 750 pg/mL in women) were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of CV mortality or HF hospitalization. Eplerenone reduces the risk of death by 24% and hospitalization by 42% in patients with moderate systolic dysfunction and NYHA class II symptoms.</p> |
| Beta-blockers: | |
| CIBIS-II (1999) | <p>Aim: To investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic heart failure.</p> <p>Study: 2647 patients with LVEF ≤ 35% in NYHA class III-IV, receiving standard therapy with diuretics and ACEIs were randomly assigned to bisoprolol (1.25 mg uptitrated to 10 mg) or placebo. Patients were followed up for a mean of 1.3 years. CIBIS-II was stopped early because bisoprolol showed a significant mortality benefit. All-cause mortality was reduced by 34% with reduction in combined CV mortality or CV hospitalization rate by 21%.</p> |
| MDC (1993) | <p>Aim: To find out whether metoprolol improves overall survival and morbidity in idiopathic dilated cardiomyopathy.</p> |

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| | <p>Study: 383 subjects with DCM (EF < 40%) were randomly assigned to metoprolol (5 mg twice daily, uptitrated to 100-150 mg daily) or placebo. 94% were in NYHA II-III, and 80% were receiving background treatment. Metoprolol prevented clinical deterioration, improved symptoms and cardiac function, and was well tolerated in patients with DCM.</p> |
| MERIT-HF (1999) | <p>Aim: To investigate whether metoprolol, in addition to standard therapy, would lower mortality in patients with reduced LVEF and HF symptoms.</p> <p>Study: 3991 patients with LVEF ≤ 40% in NYHA class II-IV and significant kidney disease, stabilised with optimum standard therapy were randomly assigned to metoprolol CR/XL (12.5 mg in NYHA III-IV or 25 mg in NYHA II uptitrated over 8 weeks to 200mg) and placebo. The primary endpoint was all-cause mortality. Long-acting metoprolol led to a 34% reduction in all-cause mortality in patients with symptomatic HFrEF with EF ≤ 40%.</p> |
| SENIORS (2005) | <p>Aim: To determine the effect of nebivolol on mortality and cardiovascular hospitalization in elderly patients with heart failure</p> <p>Study: 2128 patients ≥ 70 years, with chronic heart failure (LVEF ≤ 35% within prior 6 months or HF hospitalization within prior 12 months), NYHA II-IV; creatinine < 250 µmol/L were randomized to nebivolol (uptitrated to 10 mg) or placebo. Follow-up was for up to 40 months. Nebivolol is an effective and well-tolerated treatment for heart failure in the elderly. Combined all-cause mortality and CV hospitalization rate reduced by 14%.</p> |
| CAPRICORN (2001) | <p>Aim: To investigate the effects of carvedilol on morbidity and mortality in patients with LV dysfunction with or without heart failure after AMI.</p> <p>Study: 1959 patients with AMI and LVEF ≤ 40% were randomly assigned to carvedilol (6.25 mg) or placebo. Carvedilol reduced the frequency of all-cause and CV mortality, and recurrent non-fatal MIs.</p> |
| COPERNICUS (2002) | <p>Aim: To evaluate the effects of carvedilol on mortality (the primary endpoint) and morbidity in patients with severe heart failure</p> |

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| | <p>Study: 2289 patients with EF < 25% in NYHA class III-IV were randomly assigned to placebo or carvedilol for a mean period of 10.4 months. The addition of carvedilol to conventional therapy decreased the rate of death by 35% and the rate of death or hospitalization by 24%.</p> |
| CECCY (2018) | <p>Aim: To evaluate the role of carvedilol in preventing Anthracycline cardiotoxicity.</p> <p>Study: 200 patients with HER2-negative breast cancer tumor status and normal LVEF were randomized to receive carvedilol or placebo until chemotherapy completion. The primary endpoint was prevention of a $\geq 10\%$ reduction in LVEF at 6 months. Secondary outcomes were effects of carvedilol on troponin I, BNP, and diastolic dysfunction. Carvedilol had no impact on the incidence of early onset of LVEF reduction. However, carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction.</p> |
| COMET (2003) | <p>Aim: To compare the effect of carvedilol and metoprolol on mortality and morbidity among patients with moderate and severe CHF.</p> <p>Study: 3029 patients with EF $\leq 35\%$ in NYHA II-IV, previous CV hospitalization, and optimally treated with diuretics and ACEIs were randomly assigned to carvedilol (target dose 25 mg twice daily) and to metoprolol (target dose 50 mg twice daily). The primary endpoints were all-cause mortality and the composite endpoint of all-cause mortality or all-cause admission. Carvedilol reduced all-cause mortality compared to metoprolol tartrate.</p> |
| If channel blockers: | |
| BEAUTIFUL (2008) | <p>Aim: To test whether lowering the heart rate with ivabradine reduces CV death and morbidity in patients with CAD and LV systolic dysfunction.</p> <p>Study: 10 917 patients who had CAD and LVEF < 40% were randomized to placebo and ivabradine (5mg uptitrated to 7.5 mg twice daily). The primary endpoint was a composite of CV death, admission to hospital for AMI, and HF hospitalization. Reduction in heart rate with ivabradine does not improve cardiac outcomes in all patients with SCAD and LV systolic dysfunction, but could be used to reduce the incidence of CAD outcomes in patients who have heart rates of ≥ 70 bpm.</p> |

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| SHIFT (2010) | <p>Aim: <i>it is the first trial to specifically test the effect of isolated heart-rate reduction on outcomes in a population with heart failure.</i></p> <p>Study: <i>6558 patients with symptomatic heart failure and LVEF \leq 35% in sinus rhythm with heart rate \geq 70 b.p.m, NYHA II-IV; HF hospitalization within the previous 12 months were randomly assigned to ivabradine (titrated to 7.5 mg twice daily) or placebo. The primary endpoint was the composite of CV death or HF hospitalization. Ivabradine resulted in a 5% absolute reduction in heart failure mortality or hospitalization at 2 years.</i></p> |
| Glycosides: | |
| DIG (1997) | <p>Aim: <i>To evaluate the effect of digoxin on mortality and hospitalization in patients with chronic heart failure and normal sinus rhythm</i></p> <p>Study: <i>6800 patients with LVEF \leq 45% were randomly assigned to digoxin (median dose 0.25 mg/day) or placebo, in addition to diuretics and ACEIs with average follow-up 37 months. Digoxin reduces hospitalization rate, but does not impact mortality, among patients with HFrEF.</i></p> |
| SGLT-2 inhibitors: | |
| DAPA-HF (2019) | <p>Aim: <i>To prospectively evaluate the efficacy and safety of the dapagliflozin in patients with HFrEF, irrespective of diabetes status.</i></p> <p>Study: <i>4744 patients with NYHA II-IV, EF \leq 40% and eGFR \geq 30 mL/min/1.73 m² with or without DM were randomly assigned to receive dapagliflozin (10 mg) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening HF (hospitalization or urgent visit resulting in IV therapy for HF) or CV death. Dapagliflozin reduced rates of CV death by 18%, worsening HF by 30%, and all-cause mortality by 17%.</i></p> |
| EMPEROR-Reduced (2020) | <p>Aim: <i>To assess the safety and efficacy of empagliflozin in patients with symptomatic HFrEF, irrespective of diabetes status.</i></p> <p>Study: <i>3730 patients with NYHA II-IV, EF \leq 40% and eGFR \geq 20 mL/min/1.73 m² with or without DM were randomly assigned to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary</i></p> |

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| | <i>outcome was a composite of CV death or hospitalization for worsening HF. Empagliflozin reduced the rate of CV death or HF hospitalization by 25%, regardless of the presence or absence of diabetes.</i> |
| Isosorbide/hydralazine: | |
| V-HeFT (1986) | <p>Aim: <i>To evaluate the effects of vasodilator therapy on mortality among patients with chronic congestive heart failure</i></p> <p>Study: <i>642 Men with impaired cardiac function and reduced exercise tolerance who were taking digoxin and diuretic were randomly assigned to receive placebo, prazosin (20 mg per day), or hydralazine/isosorbide dinitrate (300/160 mg/day). Follow-up averaged 2.3 years. Addition of hydralazine and isosorbide dinitrate to the therapeutic regimen of digoxin and diuretics has a favorable effect on LV function and mortality.</i></p> |
| V-HeFT II (1991) | <p>Aim: <i>To define better the efficacy of vasodilator therapy in the treatment of chronic congestive heart failure</i></p> <p>Study: <i>The similar two-year mortality in the hydralazine isosorbide dinitrate arms in V-HeFT Trial (26%) and in V-HeFT II trial (25%), as compared with that in the placebo, and the further survival benefit with enalapril in the V-HeFT II trial (18%) strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine-isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination.</i></p> |
| A-HeFT (2004) | <p>Aim: <i>To evaluate treatment with a fixed dose of isosorbide dinitrate plus hydralazine among black patients with advanced heart failure.</i></p> <p>Study: <i>1050 men receiving digoxin and diuretic therapy for heart failure were randomly assigned to receive enalapril (20 mg/day) or hydralazine/isosorbide dinitrate (300/160 mg/day). The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival among black patients with advanced heart failure.</i></p> |
| Cardiac myosin activator: | |
| GALACTIC-HF (2021) | <p>Aim: <i>To determine the safety and efficacy of omecamtiv mecarbil in reducing the risk of cardiovascular death or heart failure events in HFrEF.</i></p> |

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| | <p>Study: 8232 patients with symptomatic chronic heart failure with $EF \leq 35\%$ and $eGFR \geq 20 \text{ mL/min/1.73 m}^2$ were randomly assigned to receive omecamtiv mecarbil or placebo, in addition to standard HF therapy. The primary outcome was a composite of a first HF event (hospitalization or urgent visit for HF) or CV death. Omecamtiv mecarbil reduced a composite of a heart-failure event or CV mortality by 8%.</p> |
| Soluble Guanylate cyclase activator: | |
| VICTORIA (2020) | <p>Aim: to evaluate vericiguat compared with placebo among patients with chronic HFrEF.</p> <p>Study: 5050 patients with chronic heart failure NYHA II-IV and $EF \leq 45\%$ with recent hospitalization and $eGFR \geq 15 \text{ mL/min/1.73 m}^2$ were assigned to receive vericiguat (target dose, 10 mg once daily) or placebo, in addition to guideline-based medical therapy. The primary outcome was a composite of CV death or first hospitalization for HF. Among patients with high-risk heart failure, vericiguat reduced CV mortality or HF hospitalization by 10%.</p> |
| Diuretics: | |
| TRANSFORM-HF (2023) | <p>Aim: To determine whether torsemide results in decreased mortality compared with furosemide among patients hospitalized for heart failure</p> <p>Study: 2859 participants hospitalized with heart failure (regardless of ejection fraction) were randomly assigned to Loop diuretic strategy of torsemide or furosemide with investigator-selected dosage. The primary outcome was all-cause mortality. Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months. However, interpretation of these findings is limited by loss to follow-up and participant crossover and nonadherence.</p> |
| Statins: | |
| CORONA (2007) | <p>Aim: To evaluate treatment with rosuvastatin in older patients with systolic heart failure.</p> <p>Study: 5011 patients aged ≥ 60 years with NYHA class II-IV ischemic, systolic heart failure were randomly assigned to receive rosuvastatin (10 mg) or placebo. The primary composite outcome was CV death, nonfatal MI, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, CV death, and the number of</p> |

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| | <i>hospitalizations. Low-dose rosuvastatin does not improve survival among patients with moderate-severe ischemic cardiomyopathy, but may reduce the rate of CV hospitalizations.</i> |
| Anticoagulation: | |
| WARCEF (2012) | <p>Aim: <i>To determine whether warfarin (with a target INR of 2-3.5) or aspirin (325 mg/day) is a better treatment for patients in sinus rhythm who have a reduced LVEF.</i></p> <p>Study: <i>2305 patients with reduced LVEF who were in sinus rhythm were randomly assigned to warfarin (with target INR of 2.0 to 3.5) or aspirin (325 mg/day) and followed up for up to 6 years. The primary outcome was the time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause. There was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The choice between warfarin and aspirin should be individualized.</i></p> |
| COMMANDER-HF (2018) | <p>Aim: <i>To assess the efficacy and safety of Rivaroxaban in reducing the risk of death, MI, or stroke in patients with HF and CAD after episode of DHF.</i></p> <p>Study: <i>5022 patients who had at least a 3-month history of chronic heart failure, LVEF ≤ 40%, and coronary artery disease and who had been treated for an episode of worsening HF within the previous 21 days were randomly assigned to receive rivaroxaban (2.5 mg twice daily) or placebo. Rivaroxaban was not associated with a significantly lower rate of death, MI, or stroke than placebo among patients with worsening chronic heart failure, reduced LVEF, coronary artery disease, and no AF.</i></p> |
| Vasopressin receptor antagonist: | |
| EVEREST-Outcomes (2007) | <p>Aim: <i>To assess the effects of tolvaptan initiated in patients hospitalized with heart failure.</i></p> <p>Study: <i>4133 patients who were hospitalized with heart failure were randomly assigned to receive oral tolvaptan (30 mg/day), or placebo for a minimum of 60 days, in addition to standard therapy. Tolvaptan initiated for acute treatment of patients hospitalized with HF had no effect on long-term mortality or HF-related morbidity.</i></p> |
| Iron deficiency in HF: | |

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| FAIR-HF (2009) | <p>Aim: To assess whether I.V ferric carboxymaltose would improve symptoms in patients who had HFrEF, and iron deficiency, with or without anemia.</p> <p>Study: 459 patients with chronic heart failure of NYHA class II or III, LVEF \leq 40% (for patients with NYHA class II) or \leq 45% (for NYHA class III), iron deficiency (ferritin level <100 $\mu\text{g/L}$ or between 100 and 299 $\mu\text{g/L}$, if the transferrin saturation was $< 20\%$), and a hemoglobin level of 95 to 135 g/L were randomly assigned to receive intravenous iron (ferric carboxymaltose 200 mg) or saline (placebo). IV iron replacement resulted in significant improvements in NYHA functional class, 6-minute walk distance, and several quality-of-life assessments.</p> |
| CONFIRM-HF (2015) | <p>Aim: To evaluate the benefits and safety of long-term i.v. ferric carboxymaltose in iron-deficient patients with heart failure.</p> <p>Study: 304 symptomatic HF patients with LVEF \leq 45%, elevated natriuretic peptides, and iron deficiency (ferritin < 100 ng/mL or 100-300 ng/mL if transferrin saturation $< 20\%$) were randomized to i.v. iron (ferric carboxymaltose) or placebo (saline) for 52 weeks. Treatment of symptomatic, iron-deficient HF patients with FCM over a 1-year period resulted in sustainable improvement in functional capacity, symptoms, and QoL and may be associated with risk reduction of HF hospitalization.</p> |
| EFFECT-HF (2017) | <p>Aim: To determine the effect of i.v. ferric carboxymaltose on exercise capacity in patients with symptomatic chronic HF and iron deficiency.</p> <p>Study: Treatment with intravenous FCM in patients with HF and iron deficiency improves iron stores. Although a favorable effect on peak VO_2 was observed on FCM, compared with standard of care in the primary analysis, this effect was highly sensitive to the imputation strategy for peak VO_2 among patients who died. Whether FCM is associated with an improved outcome in these high-risk patients needs further study.</p> |
| RED-HF (2013) | <p>Aim: To determine the efficacy of treatment of anemia with darbepoetin alfa on the composite of time to death from any cause or first hospital admission for worsening HF in patients with symptomatic LV systolic dysfunction and anemia.</p> |

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| | <p>Study: 2278 patients with systolic heart failure and mild-to-moderate anemia (hemoglobin level, 9.0 to 12.0 g/dL) were randomly assigned to receive either darbepoetin alfa (to achieve a hemoglobin target of 13 g/dL) or placebo. The primary outcome was a composite of death from any cause or HF hospitalization. Darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure and mild-to-moderate anemia.</p> |
| IRONOUT-HF (2017) | <p>Aim: To assess whether oral iron improve exercise capacity in patients with heart failure and iron deficiency</p> <p>Study: 225 adults with iron deficiency (ferritin 15-100 or 100-299 with transferrin saturation < 20%) and symptomatic HFrEF (LVEF ≤ 40% with NYHA II-IV) were randomly assigned to oral iron or placebo. Oral iron minimally repleted iron stores and had no significant effect on exercise capacity at 16 weeks compared with placebo. Oral iron replacement had no effect on exercise capacity assessed by change in peak oxygen uptake (VO₂).</p> |
| IRONMAN (2022) | <p>Aim: To assess the safety and efficacy of ferric derisomaltose (can be given as rapid, high-dose infusion) among patients with HF and iron deficiency.</p> <p>Study: 1869 patients with LVEF ≤ 45%, NYHA II–IV, with either current or recent (<6 months) HF hospitalization, elevated NT-proBNP (>250 if sinus rhythm and >1,000 if AF), and iron deficiency (Transferrin saturation <20% or ferritin <100 µg/L) were randomized in an open-label 1:1 fashion to either ferric derisomaltose or usual care. The primary outcome was CV death or HF hospitalization. I.V ferric derisomaltose was associated with a lower risk of HF hospitalization and CV death, further supporting the benefit of iron repletion in this population.</p> |
| PIVOTAL (2019) | <p>Aim: To assess the safety and efficacy of high-dose vs. low-dose iron infusion on HF events among ESRD patients.</p> <p>Study: 2141 adults undergoing maintenance hemodialysis were randomly assigned to receive either high-dose iron sucrose, administered intravenously in a proactive fashion (400 mg monthly, unless the ferritin concentration was >700 µg per liter or the transferrin saturation was ≥40%), or low-dose iron sucrose, administered intravenously in a reactive fashion (0 to 400 mg monthly, with a ferritin concentration of <200 µg per liter or a transferrin saturation of <20% being a trigger for iron administration). The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death. Among patients undergoing hemodialysis, a</p> |

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| | <i>high-dose intravenous iron regimen administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered.</i> |
| Hyperkalemia in HF: | |
| AMETHYST-DN (2015) | <p>Aim: <i>To evaluate the long-term safety and efficacy of a potassium-binding polymer, patiromer, in outpatients with hyperkalemia.</i></p> <p>Study: <i>306 outpatients with type 2 diabetes (eGFR 15 to < 60 mL/min/1.73 m² and serum K⁺ > 5.0 mEq/L) were stratified by baseline serum K⁺ into mild or moderate hyperkalemia groups and received 1 of 3 randomized starting doses of patiromer (4.2 g, 8.4 g, or 12.6 g twice daily [mild hyperkalemia] or 8.4 g, 12.6 g, or 16.8 g twice daily [moderate hyperkalemia]). Patiromer was titrated to achieve and maintain serum potassium level ≤ 5.0 mEq/L. All patients received RAAS inhibitors prior to and during study treatment. Among patients with hyperkalemia and diabetic kidney disease, patiromer starting doses of 4.2 to 16.8 g twice daily resulted in statistically significant decreases in serum potassium level after 4 weeks of treatment, lasting through 52 weeks.</i></p> |
| AMBER (2019) | <p>Aim: <i>To evaluate the use of the potassium binder, patiromer, to allow use of spironolactone in patients with CKD and resistant hypertension.</i></p> <p>Study: <i>574 patients aged ≥ 18 years with CKD (eGFR 25-45 mL/min per 1.73 m²) and uncontrolled resistant hypertension were stratified by serum potassium measurement (4.3 to < 4.7 mmol/L vs 4.7 to 5.1 mmol/L) and history of diabetes. Participants were randomly assigned to receive either placebo or patiromer (8.4 g once daily), in addition to open-label spironolactone (starting at 25 mg once daily) and their baseline blood pressure medications. In patients with resistant hypertension and CKD, patiromer enabled more patients to continue treatment with spironolactone with less hyperkalaemia. Persistent spironolactone enablement in this population of patients has clinical relevance for the treatment of resistant hypertension.</i></p> |
| DIAMOND (2021) | <p>Aim: <i>To investigate the ability of patiromer to enable specified target doses of RAAS inhibitor use in patients with HFrEF.</i></p> |

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| | <p>Study: 820 patients with HFrEF; EF \leq 40% will be started or continued on MRA titrated to 50 mg/day and other RAASi therapy to \geq 50% target dose, and patiromer. Patiromer will be titrated up to a maximum three packs/day (8.4 g/pack) to achieve optimal doses of RAASi without hyperkalemia. The primary endpoint is the mean difference in serum K⁺ from randomization between patiromer and placebo arms. Concurrent use of patiromer and high-dose MRAs reduces the risk of recurrent hyperkalemia.</p> |
| Catheter ablation for AF: | |
| CASTLE-AF (2018) | <p>Aim: To assess the effect of catheter ablation on morbidity and mortality as compared with medical therapy in patients with coexisting AF and HF.</p> <p>Study: 363 patients with symptomatic paroxysmal or persistent AF who did not have a response to antiarrhythmic drugs, had unacceptable side effects, or were unwilling to take these drugs were randomly assigned to undergo either catheter ablation or medical therapy (AF rate or rhythm control) in addition to guidelines-based therapy for HF. All the patients had NYHA class II-IV heart failure, a LVEF \leq 35%, and an ICD. Catheter ablation was associated with a significantly lower rate of a composite endpoint of all-cause mortality or HF hospitalization than medical therapy.</p> |
| AMICA (2019) | <p>Aim: To demonstrate the superiority of the catheter ablation in terms of the absolute increase in LVEF from baseline to 1 year.</p> <p>Study: 140 Patients with persistent/longstanding persistent AF and LVEF \leq 35% were randomly allocated to catheter ablation of AF (Pulmonary vein isolation) or best medical therapy (BMT). The primary study end point was the absolute increase in LVEF from baseline at 1 year. The AMICA trial did not reveal any benefit of catheter ablation in patients with AF and advanced HF. This was mainly because of the fact that at 1 year, LVEF increased in ablation patients to a similar extent as in BMT patients. The effect of catheter ablation of AF in patients with HF may be affected by the extent of HF at baseline, with a rather limited ablation benefit in patients with seriously advanced HF.</p> |
| AATAC (2016) | <p>Aim: To evaluate whether catheter ablation is superior to amiodarone for the treatment of persistent AF in patients with HF</p> |

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| | <p>Study: Patients with persistent AF, dual-chamber ICD or CRT-D, NYHA II to III, and LVEF < 40% within the past 6 months were randomly assigned to undergo catheter ablation for AF or receive AMIO. Recurrence of AF was the primary end point. All-cause mortality and unplanned hospitalization were the secondary end points. Patients were followed up for a minimum of 24 months. Catheter ablation of AF is superior to AMIO in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with HF and persistent AF.</p> |
| Surgical revascularization: | |
| STICH (2011) | <p>Aim: to evaluate the role of CABG in the treatment of patients with coronary artery disease and LV systolic dysfunction.</p> <p>Study: 1212 patients with an ejection fraction $\leq 35\%$ and CAD amenable to CABG were randomly assigned to medical therapy alone or medical therapy plus CABG. The primary outcome was the rate of death from any cause. Among patients with ischemic cardiomyopathy with LVEF $\leq 35\%$, the addition of CABG to OMT does not significantly reduce all-cause mortality after 5 years but does reduce CV-related deaths and hospitalizations. After 10 years, there is a significant reduction in all-cause mortality with CABG.</p> |
| MitraClip: | |
| COAPT (2018) | <p>Aim: To assess the safety and efficacy of transcatheter mitral leaflet approximation using MitraClip in symptomatic HF patients with secondary MR.</p> <p>Study: 614 patients with heart failure and moderate-to-severe or severe secondary MR who remained symptomatic despite the use of maximal doses of GDMT were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all cause mortality and HF hospitalizations within 24 months of follow-up. Transcatheter mitral-valve repair resulted in a lower rate of HF hospitalization and lower all-cause mortality within 24 months of follow-up than medical therapy alone.</p> |
| MITRA-FR (2018) | <p>Aim: To evaluate the clinical efficacy and safety of percutaneous mitral-valve repair in patients with HF and severe secondary MR.</p> |

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| | <p>Study: 304 patients who had severe secondary MR (defined as an EROA > 20 mm² or regurgitant volume of > 30 ml/beat), LVEF between 15 and 40%, and symptomatic heart failure were randomly assigned to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group) or to receive medical therapy alone (control group). Among patients with severe secondary MR, the rate of death or unplanned HF hospitalization at 1 year did not differ significantly between both the intervention and control groups.</p> |
| CRT and ICD | |
| See details at chapter cardiac pacing | |
| Cardiac Contractility Modulation (CCM): | |
| FIX-HF-5C (2018) | <p>Aim: To prospectively test the efficacy and safety of CCM in patients with EF ranging from 25% to 45%</p> <p>Study: 160 patients with NYHA functional class III or IV symptoms, QRS duration < 130 ms, and LVEF 25%-45% were randomized to continued medical therapy (control) or CCM (treatment, unblinded) for 24 weeks. Peak VO₂ (primary endpoint), Minnesota questionnaire, NYHA class, and 6-min walk were measured at baseline and at 12 and 24 weeks. CCM is safe, improves exercise tolerance and quality of life in the specified group of HF patients, and leads to fewer HF hospitalizations.</p> |
| Pulmonary Artery Pressure Monitoring: | |
| CHAMPION -HF (2011) | <p>Aim: to evaluate an implantable pulmonary artery pressure monitor among patients with recent hospitalization for heart failure.</p> <p>Study: Patients with NYHA class III heart failure, irrespective of the LVEF, and a recent HF hospitalization were randomly assigned to management with a wireless implantable haemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. It showed a significant reduction in HF hospitalisation for patients with NYHA class III who were managed with wireless implantable haemodynamic monitoring.</p> |
| GUIDE-HF (2021) | <p>Aim: To evaluate whether haemodynamic-guided management using remote PA pressure monitoring could reduce HF events and mortality.</p> |

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| | <p>Study: 1022 patients with all ejection fractions, NYHA functional class II-IV chronic heart failure, and either a recent HF hospitalization or elevated natriuretic peptides were randomly assigned to either haemodynamic-guided HF management based on pulmonary artery pressure or a usual care control group. Haemodynamic-guided management of HF did not result in a lower composite endpoint rate of mortality and total HF events compared with the control group in the overall study analysis.</p> |
| Telemedicine: | |
| TIM-HF2 (2018) | <p>Aim: To investigate the impact of telemedicine on unplanned CV hospitalisations and mortality in heart failure patients</p> <p>Study: 1571 eligible patients had heart failure (LVEF \leq 45%), NYHA class II or III, previous heart failure hospitalization within the last 12 months were randomly assigned to either remote patient management plus usual care or to usual care only, and were followed up for a maximum of 393 days. The primary outcome was percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death, analyzed in the full analysis set. Structured remote patient management intervention, when used in a well-defined HF population, could reduce the percentage of days lost due to unplanned CV hospital admissions and all-cause mortality.</p> |
| Exercise training programs: | |
| HF-ACTION (2009) | <p>Aim: To compare the safety and efficacy of an exercise training program in patients with NYHA class II-IV systolic CHF, with usual medical care.</p> <p>Study: 2331 medically stable outpatients with HFrEF with NYHA class II-IV systolic CHF were randomly assigned to an exercise training program and to usual medical care. The results indicate that a prescribed exercise training program in patients with chronic symptomatic systolic CHF is safe, with a modest reduction in clinical events, when added to optimal medical therapy. Although the endpoints of the trial did not meet true statistical significance, when adjusted for four confounders, they were significantly reduced in the exercise training arm compared with the usual therapy arm.</p> |
| Treatment withdrawal in HF with recovered EF: | |

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| TRED-HF (2019) | <p>Aim: To assess the safety and efficacy of withdrawal of HF medications among patients with DCM who had recovered LVEF.</p> <p>Study: 51 patients with recovered dilated cardiomyopathy were randomized to withdrawal of medication or to continuation of medications. At the completion of the study, a single arm crossover occurred where the control group who had not relapsed underwent the same medication withdrawal process. Patients with DCM whose function recovers with treatment are at increased risk of relapse at 6 months if treatment is withdrawn.</p> |
| Role of (123)I-mIBG scintigraphy in assessment of patients with HF: | |
| ADMIRE-HF (2010) | <p>Aim: To evaluate iodine-123 meta-iodobenzylguanidine (123)I-mIBG imaging for identifying symptomatic HF patients most likely to experience cardiac events.</p> <p>Study: 961 patients with NYHA II/III HF and LVEF ≤ 35% underwent (123)I-mIBG myocardial imaging and myocardial perfusion imaging then followed up for up to 2 years. ADMIRE-HF provides prospective validation of the independent prognostic value of (123)I-mIBG scintigraphy in assessment of patients with HF.</p> |

| Table 1-20: Clinical trials of HFpEF: | |
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| Trial (date) | Summary |
| ARBs: | |
| CHARM-preserved (2003) | <p>Aim: To evaluate the effects of the candesartan compared with placebo in patients with symptomatic HF and an EF > 40%.</p> <p>Study: 3023 patients with NYHA class II-IV CHF and LVEF > 40% with history of cardiac hospitalization were randomly assigned to candesartan (target dose 32 mg once daily) or placebo. Candesartan has a moderate impact in preventing admissions for CHF.</p> |
| I-PRESERVE (2008) | <p>Aim: To evaluate the effect of irbesartan on mortality and CV morbidity in patients with HFpEF.</p> |

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| | <p>Study: 4128 patients aged ≥ 60 years and LVEF $\geq 45\%$ had NYHA II-IV or NYHA II with HF hospitalization in recent 6 months were randomly assigned to receive irbesartan or placebo per day. Irbesartan did not improve the outcomes of patients with heart failure and a preserved LVEF.</p> |
| ACEIs: | |
| <p>PEP-CHF (2006)</p> | <p>Aim: To evaluate perindopril compared with placebo in patients age ≥ 70 years with clinical congestive HFpEF.</p> <p>Study: 850 patients aged ≥ 70 years with heart failure, treated with diuretics and an echocardiogram suggesting diastolic dysfunction and excluding LV systolic dysfunction or valve disease were randomly assigned to placebo or perindopril (4 mg/day) with median follow-up 2.1 years. Uncertainty remains about the effects of perindopril on long-term morbidity and mortality since this study had insufficient power for its primary endpoint. However, improved symptoms and exercise capacity and fewer HF hospitalizations in the first year were observed on perindopril.</p> |
| ARNI: | |
| <p>PARAMOUNT (2012)</p> | <p>Aim: To assess the safety and efficacy of Sacubitril/valsartan in patients with HFpEF.</p> <p>Study: 283 patients with NYHA class II-III heart failure, LVEF $\geq 45\%$, and NT-proBNP > 400 pg/mL were randomly assigned to Sacubitril/valsarta (titrated to 200 mg twice daily) or valsartan (titrated to 160 mg twice daily), and treated for 36 weeks. Sacubitril/valsarta reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.</p> |
| <p>PARAGON-HF (2019)</p> | <p>Aim: To assess the effect of sacubitril-valsartan on HF hospitalizations and CV mortality among patients with HF and EF $\geq 45\%$.</p> <p>Study: 4822 patients with NYHA class II-IV heart failure, LVEF $\geq 45\%$, LA enlargement or LVH AND elevated BNP ≥ 300 pg/mL or NT proBNP ≥ 900 pg/mL or HF hospitalization in the last 9 months were randomly assigned to receive sacubitril-valsartan (target dose, 97/103 mg twice daily) or valsartan (target dose, 160 mg twice daily). Sacubitril-valsartan did not result in significantly lower rate of HF hospitalizations and CV mortality.</p> |

| Mineralocorticoid Antagonist: | |
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| Aldo-DHF (2013) | <p>Aim: To assess the efficacy and safety of long-term spironolactone in HFpEF.</p> <p>Study: 422 ambulatory patients ≥ 50 years with NYHA class II or III heart failure, LVEF $\geq 50\%$, peak $VO_2 \leq 25$ mL/min/kg and evidence of diastolic dysfunction were randomly assigned to receive spironolactone (25 mg once daily) or placebo with 12 months of follow-up. Spironolactone improved LV diastolic function (E/e' decreased from 12.7 to 12.1) but did not affect maximal exercise capacity, patient symptoms, or quality of life in patients with HFpEF.</p> |
| TOPCAT (2014) | <p>Aim: To evaluate the effects of spironolactone in patients with HFpEF.</p> <p>Study: 3445 patients ≥ 50 years with symptomatic heart failure and LVEF $\geq 45\%$, HF hospitalization within recent 12 months, or BNP ≥ 100 pg/mL or NT-proBNP ≥ 360 pg/mL were randomly assigned to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of CV mortality, aborted cardiac arrest, or HF hospitalization. Spironolactone does not reduce the composite endpoint of CV mortality, aborted cardiac arrest, or HF hospitalizations when compared to placebo in patients with HFpEF.</p> |
| SGLT2 inhibitors: | |
| EMPEROR-Preserved (2021) | <p>Aim: To evaluate the effects of empagliflozin on major heart failure outcomes in patients with HFpEF.</p> <p>Study: 5988 patients with class II-IV heart failure and LVEF $> 40\%$ were randomly assigned to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of CV death or HF hospitalization. Empagliflozin reduced the combined risk of CV death or HF hospitalization in patients with HFpEF, regardless of the presence or absence of diabetes.</p> |
| DELIVER (2022) | <p>Aim: To evaluate if dapagliflozin would reduce the risk of HF worsening or CV death among patients with a mildly reduced or preserved LVEF.</p> <p>Study: 6263 patients with heart failure and a LVEF $> 40\%$ were randomly assigned to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite</p> |

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| | <i>of HF worsening or CV death. Dapagliflozin reduced the combined risk of HF worsening or CV death among patients with heart failure and a mildly reduced or preserved ejection fraction.</i> |
| Other drugs: | |
| Ancillary DIG (DIG-PEF) (2006) | <p>Aim: <i>To assess the effect of digoxin on the HF hospitalization or HF mortality in patients with normal sinus rhythm and EF > 45%.</i></p> <p>Study: <i>988 ambulatory chronic heart failure patients with normal sinus rhythm and EF > 45% were randomly assigned to digoxin or placebo. Digoxin had no effect on all-cause or cause-specific mortality or on all-cause or CV hospitalization.</i></p> |
| RELAX (2013) | <p>Aim: <i>To determine the effect of the sildenafil compared with placebo on exercise capacity and clinical status in HFPEF.</i></p> <p>Study: <i>216 stable outpatients with HF, LVEF ≥ 50%, elevated NT-proBNP or elevated invasively measured filling pressures, and reduced exercise capacity (peak VO₂ < 60% of reference values) were randomized to sildenafil (administered orally at 20 mg, 3 times daily for 12 weeks, followed by 60 mg, 3 times daily for 12 weeks) or placebo. Sildenafil did not result in significant improvement in exercise capacity or clinical status.</i></p> |
| NEAT-HFpEF (2015) | <p>Aim: <i>to evaluate treatment with a long-acting nitrate compared with placebo among patients with HFpEF.</i></p> <p>Study: <i>110 patients with HFpEF were randomly assigned to a 6-week dose escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level. Patients with HFpEF who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than did patients who received placebo.</i></p> |
| PIROUTTE (2021) | <p>Aim: <i>To evaluate pirfenidone, an antifibrotic agent, compared with placebo among patients with HFpEF.</i></p> <p>Study: <i>94 patients with HFpEF were randomized to pirfenidone versus placebo. Among patients with HFpEF, pirfenidone appeared to be beneficial. It was associated with a modest reduction in myocardial fibrosis, as assessed by cardiac MRI, compared with placebo. The clinical significance of this finding is unknown.</i></p> |

References and Suggested readings:

- McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2023 Oct 1;44(37):3627-39.
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- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier.

Chapter 2:

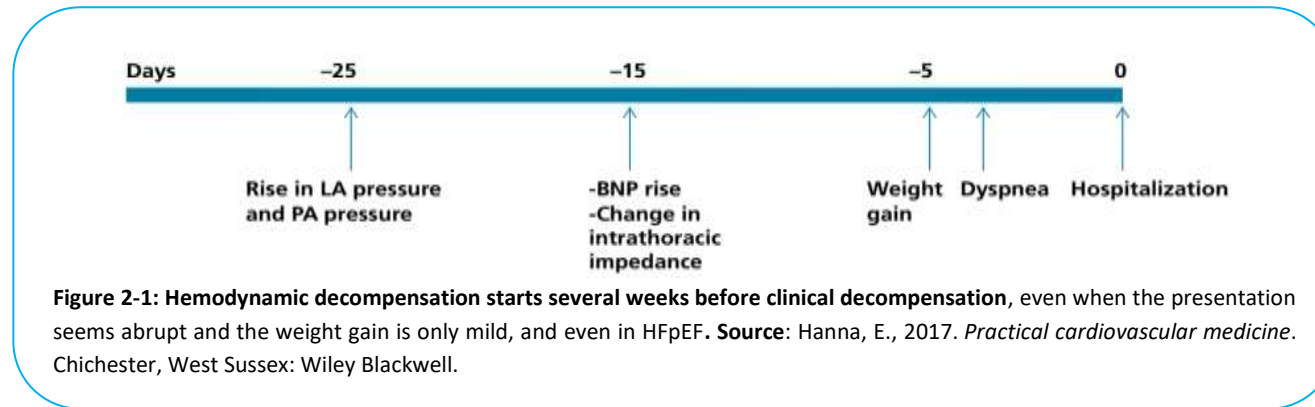
Acute Heart Failure

AHF refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit.

Acute HF presentation encompasses three syndromes:

- 1. Acutely decompensated HF (ADHF)**, due to deterioration of a chronic compensated HF. ADHF is the most common form of acute HF presentation (50-70%). The underlying causes are the same as chronic HF, with decompensating triggers.
- 2. De novo acute HF**, due to acute myocardial dysfunction (ischaemic, inflammatory or toxic), or acute valve insufficiency. Approximately 25% of acute HF presentations are de novo acute HF.
The LV is not as dilated in these cases as it is in chronic HF and ADHF. The accompanying pulmonary edema is called flash pulmonary edema. De novo HF, but also many cases of ADHF, develop abruptly and only have mild volume overload: there is volume redistribution more than volume overload.
Compared to patients with acutely decompensated CHF, those with new onset HF may have a higher in-hospital mortality but have lower post-discharge mortality and rehospitalization rates.
- 3. Heart failure *secondary to a chronic severe systolic HF*** with a relentless and progressive deterioration of a low-output state. It represents a small proportion of acute HF presentations (~5%).

N.B: ~50% of patients who present with acute HF have systolic HF; the rest have HFpEF.



Triggers of acute decompensation:

- **Non-compliance with medical therapy, salt and fluid restriction.**
- **Hypertensive emergency:** The abnormal vascular compliance leads to marked blood pressure lability with relatively minor changes in the intravascular volume; this causes a precipitous increase in afterload and decompensates LV failure. Bilateral renal artery stenosis is underlying a few of these cases, particularly unexplained recurrent ADHF.
Acute hypertension may at least partly be the result of the acute pulmonary edema and the sympathetic surge. This explains the precipitous blood pressure fall commonly seen with initiation of diuresis.
While vasodilatation increases stroke volume of the failing heart, excessive vasodilatation, seen sometimes in patients who get intubated and sedated, may not be matched by enough rise in cardiac output, as the cardiac reserve is limited, which leads to precipitous hypotension. Thus, the aggressive initiation of vasodilators or antihypertensive drugs should be avoided until diuresis has been started.
- **Acute ischemia/ACS:** ACS is responsible for up to 30% of acute HF presentations, especially de novo HF; CAD without ACS is documented in another ~30% of patients with acute HF. Diffuse ischemia may lead to acute diastolic dysfunction, systolic dysfunction, or ischemic MR.

- **Arrhythmias**, such as AF with a rapid ventricular rate. Approximately 30-40% of patients with ADHF have AF. The occurrence or the acceleration of AF can be secondary to HF rather than the cause of HF.

N.B: A patient with decompensated HF typically has an elevated rate (80-110 bpm). *AV block or sinus bradycardia*, even at a rate of 50-60 bpm, is inappropriate and signifies that the bradyarrhythmia is a factor underlying HF decompensation (bradycardia further reduces cardiac output).

- **Acute mechanical cause underlying AHF:** This may present as a mechanical complication of ACS (free wall rupture, ventricular septal defect, acute mitral regurgitation), or chest trauma, or as acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis and comprise rare causes of obstruction (e.g. cardiac tumours).
- **Any systemic infection; anemia.** Normally, during infectious states and chronic anemia, both preload and inotropism increase, allowing cardiac output to increase and match the high metabolic demands. This is similar to the physiology of exercise.
- Increased sympathetic drive, **stress-related cardiomyopathy**.
- **Drug-induced** (alcohol, NSAIDs, steroids, recreational drugs, and cardiotoxic chemotherapeutics).

In systolic or diastolic dysfunction, three untoward effects occur:

1. LV is unable to accommodate the increased preload and fails, leading to increased filling pressures;
2. The stroke volume cannot increase enough to match the dilated circulation, which reduces tissue perfusion;
3. The incumbent tachycardia may decompensate HF.

Notes:

- 40-50% of acute heart failure episodes have no known precipitant.
- On admission, 30-64% of acute HF patients have moderate or severe renal failure. This may be either a cause of HF (acute tubular necrosis, intrinsic renal disease) or, more often, a result of HF. Either way, renal failure worsens the volume overload and leads to further neurohormonal activation, and ultimately worsening HF, which leads to a vicious circle of mutual HF-renal damage.

Classification:

| Table 2-1: Classification of acute heart failure according to Clinical presentation: | | | | |
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| | Acute decompensated heart failure | Acute pulmonary oedema | Isolated RV failure | Cardiogenic shock |
| Main mechanisms | -LV dysfunction -Sodium and water retention | - Increased afterload and/or LV diastolic dysfunction - Valvular heart disease | -RV dysfunction and/or precapillary pulmonary hypertension | -Severe cardiac dysfunction |
| Main cause of symptoms | Fluid accumulation, increased intraventricular pressure | Fluid redistribution to the lungs and acute respiratory failure | Increased central venous pressure and often systemic hypoperfusion | Systemic hypoperfusion |
| Onset | Gradual (days) | Rapid (hours) | Gradual or rapid | Gradual or rapid |
| Main haemodynamic abnormalities | - LVEDP and PCWP: Increased ⁽¹⁾ -Cardiac output: Low or normal -SBP: Normal to low | -LVEDP and PCWP: Increased -Cardiac output: Normal -SBP: Normal to high | -RVEDP: Increased -Cardiac output: Low -SBP: Low | - LVEDP and PCWP: Increased - Cardiac output: Low - SBP: Low |
| Main clinical presentations | -Wet and warm <u>or</u> -Wet and cold | - Wet and warm | -Wet and cold | -Wet and cold |
| Main treatment | -Diuretics | - Diuretics - Vasodilators | -Diuretics for peripheral congestion | -Inotropic agents/vasopressors |

(1) May be normal with low cardiac output.

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| | <i>-Inotropic/vasopressors (if peripheral hypoperfusion) -Short-term MCS or RRT if needed.</i> | | <i>-Inotropic/vasopressors (if peripheral hypoperfusion) -Short-term MCS or RRT if needed.</i> | <i>-Short-term MCS -RRT</i> |
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Clinical picture/Profiles:

A. Always assess for:

1. Congestion, also known as “wet or dry” picture:

- Orthopnea (90% sensitive), crackles (uncommon), peripheral edema, pleural effusions, ascites.
- Elevated JVP, S3, loud P2 that is heard at the lower left sternum or apex (usually with split S2).
- Also, the lack of a 30% decrease of the systolic and pulse pressure during the strain phase of Valsalva’s maneuver is a highly sensitive and specific (~90%) sign of volume overload ⁽¹⁾.

2. Peripheral perfusion, also known as “warm or cold” picture: Cold HF has worse prognosis, with a mortality that is twice as high as “warm” HF. **Cold signs are:**

- Borderline or low SBP (< 90-100 mmHg), narrow pulse pressure (pulse pressure < 25% SBP, reflecting a reduced stroke volume), or pulsus alternans. A narrow pulse pressure is the most sensitive and specific finding in low stroke volume.
- Cool and/or cyanotic extremities.
- Severe fatigue, drowsiness, Cheyne-Stokes respiration.
- Severe worsening of renal failure.
- Hyponatremia.

(1) This is done using continuous non-invasive pressure monitoring and a 10-15s strain; alternatively, using a BP cuff inflated at systolic pressure or slightly above it, Korotkoff sounds remain heard throughout the strain phase of Valsalva and do not overshoot after the release.

- Poor or no response to diuretics.

B. Classification: based on *hemodynamic profiles* (Congestion and Perfusion):

- **Wet and warm:** pulmonary/peripheral edema without signs of low cardiac output. This is the most common ADHF profile (~2/3 of the cases).
- **Wet and cold:** pulmonary/peripheral edema with signs of low cardiac output (~30% of the cases). Hypotension is present in only 2% of acute HF.
- **Dry and cold:** low output is present without edema. This may be due to hypovolemia, or to a euvolemic severe HF (~5% of acute HF), in which case it portends the worst ADHF prognosis.

N.B: Patients with HF complicating AMI can be classified according to **Killip Classification** into:

- **Class I:** No clinical signs of HF.
- **Class II:** HF with rales and S3 gallop.
- **Class III:** Frank acute pulmonary oedema.
- **Class IV:** Cardiogenic shock, hypotension (SBP < 90 mmHg) and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis.

Investigations:

- **Chest X-ray:** Pulmonary venous congestion, pleural effusion, interstitial or alveolar oedema and cardiomegaly are the most specific findings for AHF, although in up to 20% of patients with AHF, chest X-ray is nearly normal. Supine chest radiographs are of limited value in AHF. Chest X-ray is also useful to identify alternative non-cardiac diseases that may cause or contribute to the patient's symptoms (i.e., pneumonia, non-consolidative pulmonary infections).
- **Lung ultrasound (LUS):** In comparison to chest X-ray, LUS is better in ruling out interstitial oedema and pleural effusions. LUS detects B-lines originating from extravasated fluid into the interstitium and alveoli. More than three B-lines in more than two

intercostal spaces bilaterally are considered diagnostic for the detection of interstitial and alveolar oedema in acute heart failure. The number of B-lines increases with the severity of congestion and facilitates monitoring of response to treatment.

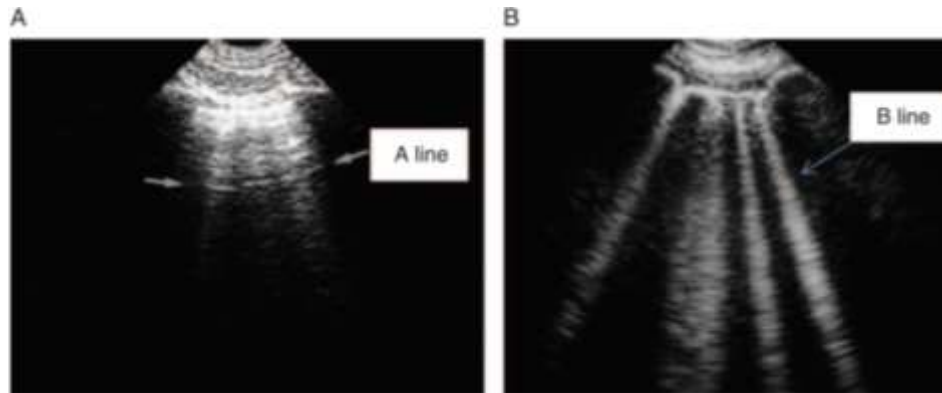


Figure 2-2: Lung ultrasound in normal and AHF patients. (A) From the pleural line, one repetition of the pleural line, a horizontal line [A line], parallel to the pleural line, is visible, indicating normal lung with no pulmonary edema. Arrows indicate A lines. Note some ill-defined vertical comet-tail artifacts, not to be confused with B lines. **(B)** Four or five B-lines arise from the pleural line. B lines are vertical, long, well-defined artifacts erasing the A-lines and moving in concert with lung sliding. B lines indicate pulmonary edema. **Source:** Whole Body Ultrasonography in the Critically Ill, Springer 2010.

- **ECG** is rarely normal in AHF (high negative predictive value). It is also helpful in identifying underlying cardiac disease and potential precipitants (rapid AF, acute myocardial ischaemia).
- **Echocardiography:**
 - It is mandatory only in patients with haemodynamic instability (particularly in cardiogenic shock) and in patients suspected of acute life-threatening cardiac abnormalities (mechanical complications, acute valvular regurgitation and aortic dissection).
 - Early echocardiography should be considered in all cases with de novo AHF and in those with unknown cardiac function; however, the optimal timing is unknown (preferably within 48 h from admission).

- With rising filling pressures, an increase in early diastolic mitral inflow velocities (E wave) occurs. This is indicative of increased filling pressures in the presence of a low e' , especially if E-wave deceleration time is short and A-wave velocities are low. Nevertheless, the use of e' might be limited in advanced heart failure.
- Global longitudinal strain (GLS) is recommended by EACVI for the evaluation of cardiac performance in all AHF patients, indicating mild and severe dysfunction if reduced $\leq 16\%$ and $\leq 10\%$, respectively.

○ **Laboratory tests:**

- **Natriuretic peptides:** Plasma NP level (BNP, NT-proBNP or MR-proANP) should be measured in all patients with acute dyspnea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnea. Normal concentrations of NPs make the diagnosis of AHF unlikely. Cut-offs for acute HF are: BNP < 100 pg/mL, NT-proBNP < 300 pg/mL and MR-proANP < 120 pg/mL. Unexpectedly low NPs can be seen in some patients with advanced HF, flash pulmonary oedema or right sided AHF.

In most patients with acute HF, BNP decreases with diuresis and the reduction of LV filling pressure but may not return to normal, as the LV remains dilated even after LVEDP is normalized (called residual, dry BNP). Also, the reduction in BNP may be delayed due to reduced clearance, especially in renal failure. *Thus, daily BNP measurements are not warranted; when clinical euvolemia is established, a pre-discharge BNP level may be determined and used in follow-up.* A persistently elevated BNP upon discharge is a predictor of HF readmission and has a negative prognostic value.

- Cardiac troponin ⁽¹⁾, BUN, creatinine, electrolytes (sodium, potassium), liver function tests, TSH, glucose and complete blood count; D-dimer is indicated in patients with a suspicion of acute pulmonary embolism. Soluble CD146, adrenomedullin and carbohydrate antigen-125 (CA-125) ⁽²⁾ are novel biomarkers more precisely reflecting vascular congestion.
- Routine arterial blood gas is not needed and should be restricted to patients in whom oxygenation cannot be readily assessed by pulse oximetry.

N.B:

- ☞ It is recommended to measure creatinine, BUN and electrolytes every 1-2 days during hospitalization and before discharge.
- ☞ Hyponatremia usually signifies advanced low-output HF or hemodilution from hypervolemia. Outpatient hypernatremia signals dehydration and is very unusual in acute HF.
- ☞ Liver function tests are often impaired in patients with AHF due to haemodynamic derangements (both reduced output and increased venous congestion).

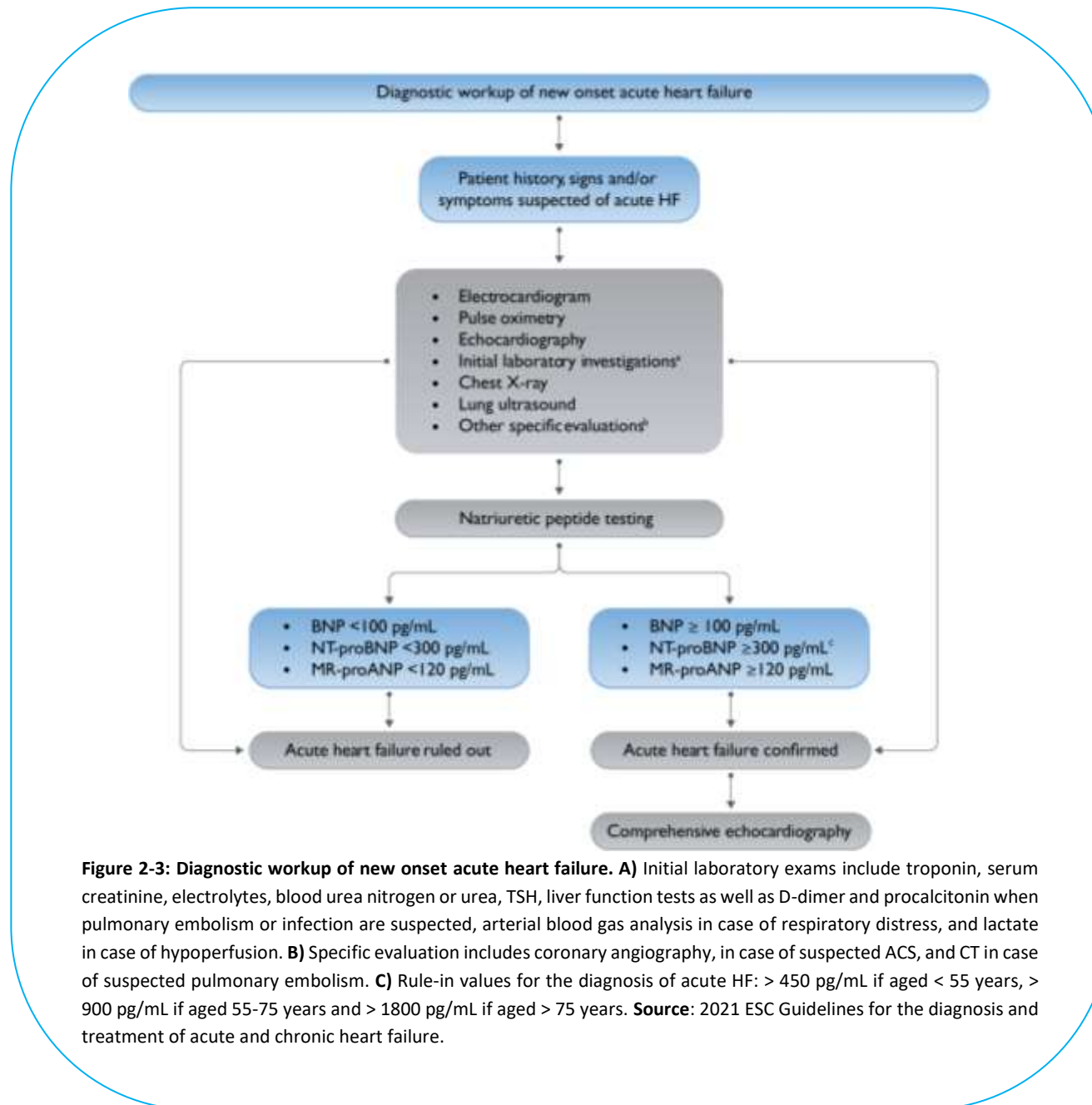
(1) *Measurement of cardiac troponins is useful for detection of ACS as the underlying cause of AHF. However, elevated cardiac troponins are detected in the vast majority of patients with AHF even in absence of any thrombotic coronary event. This occurs due to increased LVEDP in patients with acute HF, leading to microcirculatory coronary compression and reduction of the pressure gradient between the aortic pressure and LVEDP, i.e., the pressure gradient that drives coronary microcirculatory flow. Troponin is a marker of increased mortality in acute HF independent of coronary disease.*

(2) *CA-125 may help diuretic dosing and titration during hospitalization or following stabilization from acute HF (targeting ≤ 35 U/mL). CA-125 was first identified in an ovarian cancer, but was subsequently found to be expressed on the surface of cells derived from coelomic epithelium, including pleural and epicardial linings. In addition to its use in detection of and prognostication for ovarian malignancy, CA-125 has also been shown to be elevated in a wide range of non-gynaecological conditions especially related to volume expansion, including cirrhosis, renal failure, and HF. Although the precise mechanisms have not been elucidated, it is postulated that congestive HF may raise hydrostatic pressure that can lead to mechanical stretch of the mesothelium (pericardium, pleura, and peritoneum) and third space fluid retention, with resultant inflammation and cytokines release. RV dilatation has been noted to be the strongest echocardiographic predictor for elevated CA-125 level.*

| Table 2-2: Diagnostic tests in patients with acute heart failure: | | | |
|---|---|------------------------------------|-------|
| Exam | Time of measurement | Diagnostic value | Class |
| Routine tests: | | | |
| Serum troponin | Admission | Exclusion of ACS | I |
| Natriuretic peptides (BNP, NT-proBNP, MR-proANP) | Admission, pre-discharge | High negative predictive value | IIa |
| ECG | Admission, during hospitalization, pre-discharge | Exclusion of ACS or arrhythmias | I |
| Echocardiography | | Major | I |
| Lung US | | Confirmatory | IIb |
| Chest-X ray | Admission, during hospitalization | Confirmatory | IIb |
| For Prognostic assessment and treatment: | | | |
| Serum creatinine | Admission, during hospitalization, pre-discharge | None | I |
| Serum electrolytes (Na, K, Cl) | | | I |
| Iron status (transferrin, ferritin) | Pre-discharge | | I |
| For assessment of causes and comorbidities: | | | |
| TSH | | None | I |

| | | | |
|--|-----------------------------------|--|--|
| | Admission | | (If hypo hyperthyroidism suspected) |
| D-dimer | | Useful to exclude pulmonary embolism | I (If pulmonary embolism is suspected) |
| Procalcitonin | | Useful for diagnosis of pneumonia | IIb (If pneumonia is suspected) |
| Lactate | Admission, during hospitalization | Useful to assess perfusion status ⁽¹⁾ | I (If peripheral hypoperfusion is suspected) |
| Pulse oximetry and arterial blood gas | | Useful to assess respiratory function | I (If respiratory failure is suspected) |

(1) An abnormal serum lactate > 2 mmol/L is associated with higher mortality in AHF. Further, levels that do not decrease following appropriate treatment are associated with a poor outcome. Lactate levels should therefore be assessed on admission in unstable or hypoxaemic patients with AHF, and repeated at short intervals (initially e.g., every 1-2 h) during the acute phase.

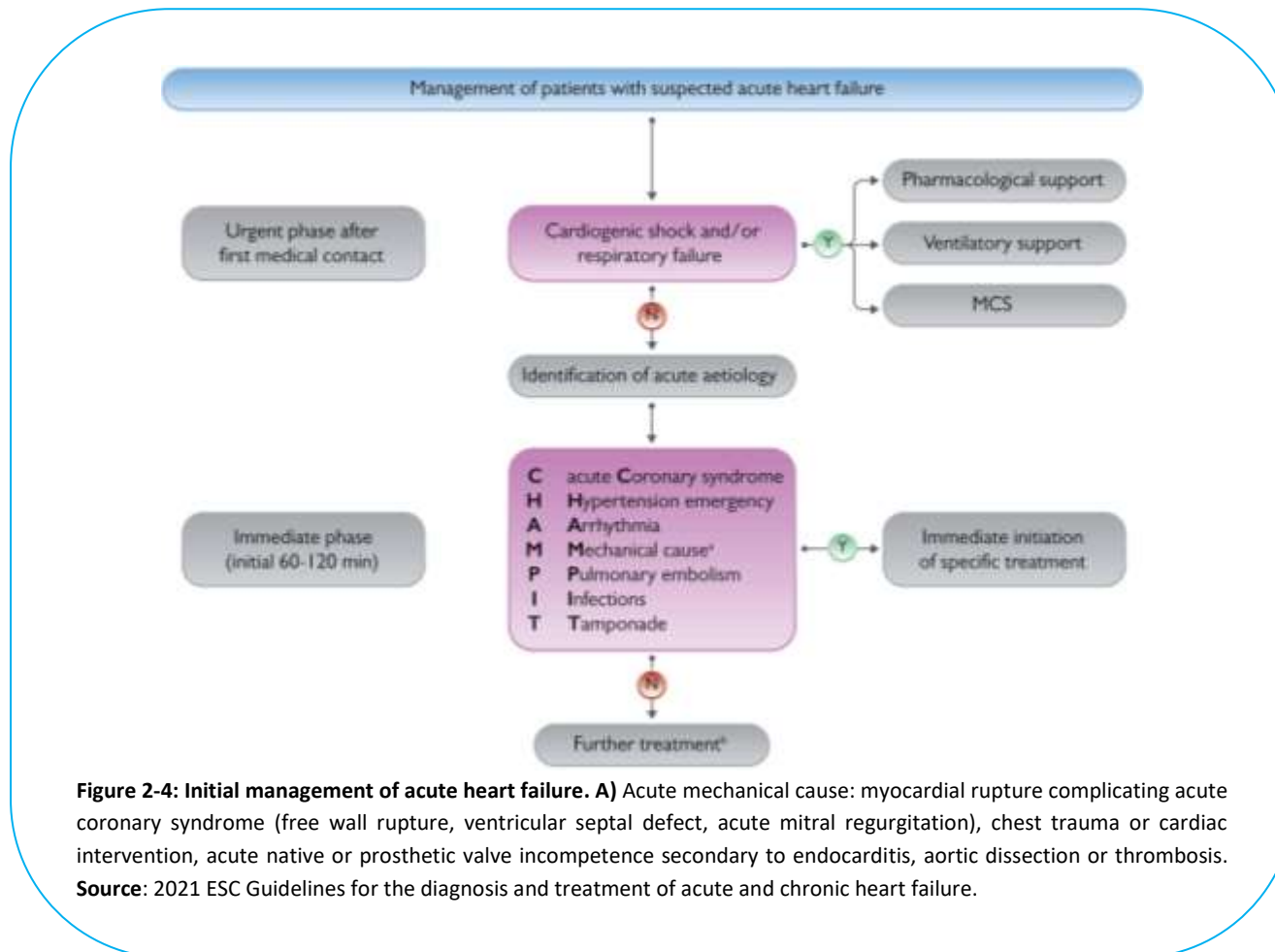


Treatment:

The target is stabilization, diagnosis, symptoms relief and identification of triggers of AHF.

Management of AHF consists of:

- 1. Urgent care**
- 2. Hospitalization**
- 3. Discharge**



▪ **Urgent Care:**

- Pulse oximetry, BP, heart rate, respiratory rate, and continuous ECG, should be instituted immediately.

- In AHF, oxygen should not be used routinely in non-hypoxaemic patients (unless SaO_2 is $< 90\%$), as it causes vasoconstriction and a reduction in cardiac output. In COPD, hyperoxygenation may increase ventilation–perfusion mismatch, suppressing ventilation and leading to hypercapnia.
- CPAP or BiPAP may be acutely used in patients with respiratory distress, respiratory rate > 25 breaths/min and $\text{SaO}_2 < 90\%$, as a bridge until pulmonary edema is relieved with diuretics. CPAP or BiPAP should only be tried in a patient with appropriate level of wakefulness who is not severely hypoxic or acidotic ($\text{pH} > 7.2$), and not hypotensive. It should be quickly removed within < 30 min if it proves ineffective as its prolonged ineffective use may paradoxically increase and prolong respiratory work, gastric distension and aspiration, and delay a salutary intubation.
- Intubation is required in patients with severe respiratory distress if CPAP/BiPAP and furosemide have not been effective quickly. Intubation with positive-pressure ventilation leads to:
 - \downarrow Venous return $\rightarrow \downarrow$ RV preload $\rightarrow \downarrow$ LV preload.
 - \downarrow LV afterload (\downarrow systolic wall stress): a positive intrathoracic pressure surrounding the myocardium negates some of the intracavitary pressure and reduces the tension against the inner myocardial wall.
 - \uparrow Pulmonary vascular resistance $\rightarrow \uparrow$ RV afterload \rightarrow RV enlargement $\rightarrow \downarrow$ LV Compliance.
 - \downarrow Systemic BP $\rightarrow \downarrow$ Cardiac output (but in patients with AHF with elevated LV preload and afterload, cardiac output may increase as consequence of the application of positive intrathoracic pressure).

Conversely, extubation may be poorly tolerated in HF patients or patients with critical CAD, as it drastically increases both preload and afterload.

Caution should be exercised with regard to side effects of anaesthetic drugs, among which propofol can induce hypotension and have cardiodepressive side effects. In contrast, midazolam may have fewer cardiac side effects and thus is preferred in patients with AHF or cardiogenic shock.

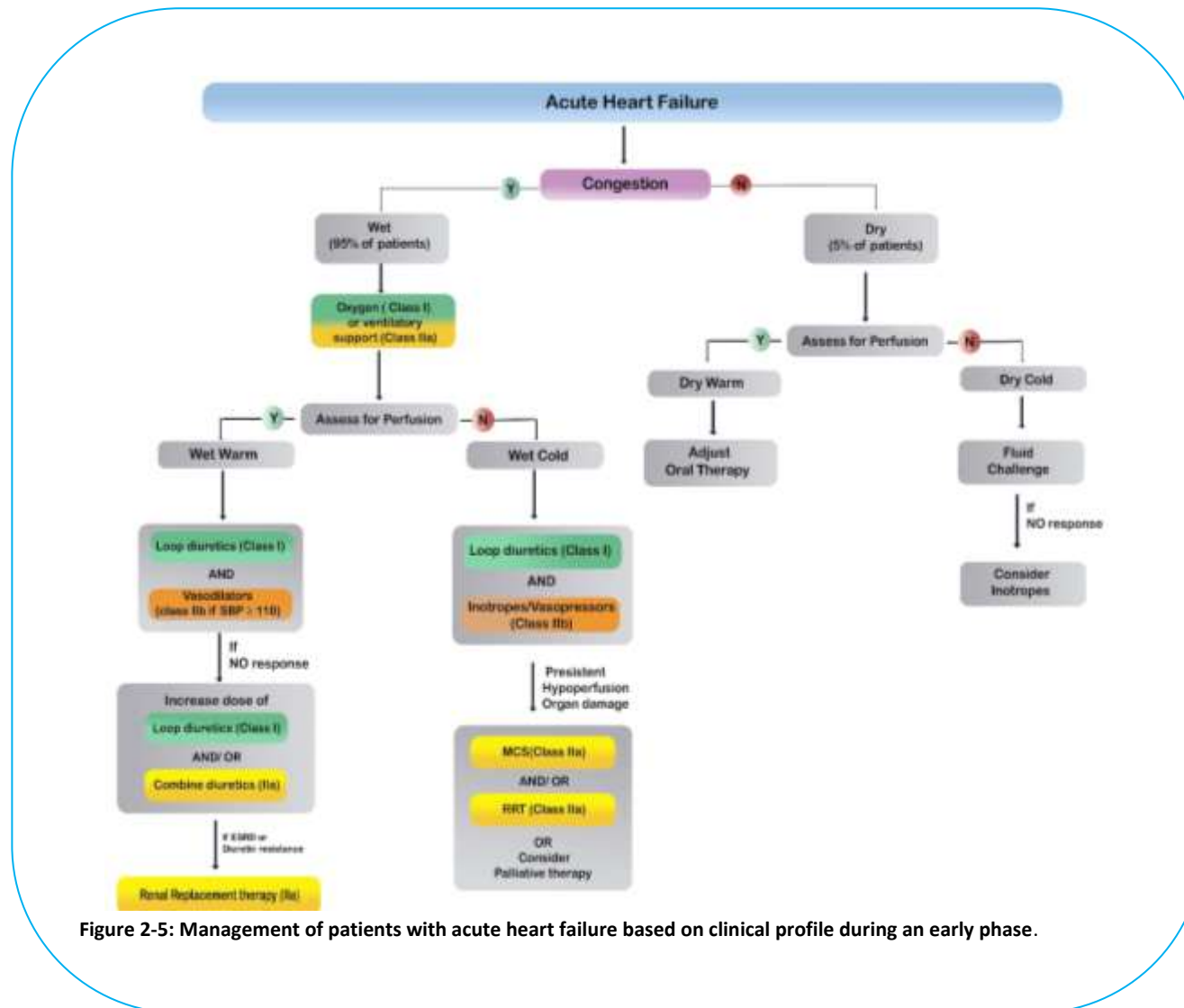


Figure 2-5: Management of patients with acute heart failure based on clinical profile during an early phase.

▪ **Hospitalization:**

- **Criteria for ICU/CCU admission:** include any of the following:

- Need for intubation (or already intubated).
- Signs/symptoms of hypoperfusion.
- Oxygen saturation (SaO_2) < 90% (despite supplemental oxygen).
- Use of accessory muscles for breathing, respiratory rate > 25/min.
- Heart rate < 40 or > 130 bpm, SBP < 90 mmHg.

The remaining patients with AHF usually need hospitalization on an ordinary ward.

Only a few patients admitted to the ED with AHF (mainly as exacerbation of HF symptoms with subtle signs of congestion) after a small dose of diuretics and some adjustments of oral therapy can be discharged directly home from the ED with advice to be clinically followed in an outpatient clinic. Patients with de novo AHF should not be discharged home from ED.

- **Diagnosis and treatment of triggers:**

- **Acute coronary syndrome:** Coexistence of these two clinical conditions (ACS and AHF) always identifies a very-high-risk group where an immediate (i.e., < 2 hr from hospital admission in patients with NSTEMI) invasive strategy with intent to perform revascularization is recommended.
- **Hypertensive emergency:** AHF precipitated by rapid and excessive increase in BP typically manifests as acute pulmonary oedema. Aggressive BP reduction (in the range of 25% during the first few hours and cautiously thereafter) with i.v. vasodilators in combination with loop diuretics is recommended.
- **Tachyarrhythmias or severe bradycardia/conduction disturbance:**
Electrical cardioversion is recommended if atrial or ventricular arrhythmia is thought to be contributing to the haemodynamic compromise. In selected cases, immediate angiography ± revascularization and radiofrequency ablation may be considered.
- **Acute mechanical cause underlying AHF:** Echocardiography is essential for diagnosis, and treatment typically requires circulatory support with surgical or percutaneous intervention.
- **Acute pulmonary embolism:** if confirmed as the cause of shock or hypotension, primary reperfusion is recommended either with thrombolysis, catheter-based approach or surgical embolectomy.

N.B:

- ☞ Even when ACS is not suspected, a coronary angiogram needs to be performed as part of acute or severe HF workup, unless previously done; it is preferably performed during the index HF hospitalization before discharge, after appropriate diuresis. In one analysis, patients with acute HF and CAD who did not undergo revascularization before discharge had a significantly higher 60-90-day mortality than patients without CAD, whether EF was low or preserved; this excess in mortality was abolished with revascularization performed during hospitalization (OPTIMIZE-HF registry).
- ☞ In decompensated HF, dyspnea is frequently described as chest tightness; thus, acutely, chest tightness does not equate with angina and is not a specific marker of CAD.
- ☞ In AF: while a rate of 100-120 bpm may trigger HF decompensation, this rate is appropriate once the patient is in decompensated HF and allows an increase in cardiac output and left atrial emptying.
Aggressive acute rate control (< 80 bpm) may be harmful as it may reduce cardiac output, and should be attempted later when HF has been diuresed and stabilized.
AF may convert or slow down spontaneously with HF therapy and with reduction of LA pressure. Along with diuresis, digoxin may be started for rate control, followed by β -blocker after initial stabilization.

Table 2-3: ESC Recommendations for the initial treatment of acute heart failure:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Oxygen and ventilatory support: | | |
| <i>Oxygen is recommended in patients with SpO₂ < 90% or PaO₂ < 60 mmHg.</i> | I | C |
| <i>Non-invasive positive pressure ventilation should be considered in patients with respiratory distress (respiratory rate > 25 breaths/min, SpO₂ < 90%) and started as soon as possible to decrease respiratory distress and reduce the rate of endotracheal intubation.</i> | IIa | B |
| <i>Intubation is recommended for progressive respiratory failure persisting in spite of oxygen administration or non-invasive ventilation.</i> | I | C |
| Diuretics: | | |
| <i>Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.</i> | I | C |
| <i>Combination of a loop with thiazide diuretics should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.</i> | IIa | B |
| Vasodilators: | | |
| <i>In patients with AHF and SBP > 110 mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion.</i> | IIb | B |
| Inotropic agents: | | |
| <i>Inotropic agents may be considered in patients with SBP < 90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function.</i> | IIb | C |

| | | |
|--|------------|----------|
| <i>Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.</i> | III | C |
| Vasopressors: | | |
| <i>A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion.</i> | IIb | B |
| Other drugs: | | |
| <i>Thromboembolism prophylaxis (e.g., with LMWH) is recommended to reduce the risk of deep venous thrombosis and pulmonary embolism.</i> | I | A |
| <i>Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety ⁽¹⁾.</i> | III | C |

▪ **Discharge:**

○ **Criteria for discharge:**

- Treatment of exacerbating factors.
- Patients need to achieve near optimal volume before discharge. They should be able to ambulate without dizziness and with minimal dyspnea.
- Transition from intravenous to oral diuretic needs to be completed and stable for 12-24 hrs before discharge. Oral diuretic dose should maintain a slightly negative input/output balance (Total oral furosemide dose is numerically 0.5-0.75 the I.V dose used).
- Around 25-30% of patients with AHF are discharged with persistent signs/symptoms of congestion and/or minimal or no weight loss as demonstrated by elevated NP levels, provoked orthopnoea, paradoxical changes of SBP in orthostasis or at Valsalva manoeuvre, and a poor 6-min walk test.

(1) Retrospective analyses suggest that morphine administration is associated with a greater frequency of mechanical ventilation, prolonged hospitalization, more ICU admissions, and increased mortality.

- Persistent congestion before discharge is associated with a higher risk of readmission and mortality. Thus, monitoring changes in NTproBNP levels, hemoconcentration and renal function is recommended. Both reduction in NTproBNP levels by at least 30% and hemoconcentration is associated with reduced post-discharge mortality and rehospitalization rate. Despite worsening renal functions, patients with hemoconcentration have greater weight loss, and greater reduction in RA pressure and PCWP.
- **First Follow-up visit:** It is recommended to have one follow-up visit within 1-2 weeks after discharge. To assess signs and symptoms of HF, volume status, BP, heart rate, and laboratory work-up including renal function, electrolytes, and possibly NPs. Iron status and hepatic function should be assessed if not done before discharge.

| Table 2-4: ESC Recommendations for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart Failure: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.</i> | I | C |
| <i>An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death ⁽¹⁾.</i> | I | B |
| <i>An early follow-up visit is recommended at 1-2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy.</i> | I | C |
| <i>Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin < 100 ng/mL <u>or</u> serum ferritin 100-299 ng/mL with TSAT < 20%, to improve symptoms and reduce rehospitalizations.</i> | IIa | B |

(1) This recommendation is based on the STRONG-HF trial. In this trial, the use of ACE-I/ARB/ARNI, beta-blockers, and MRA was evaluated in patients with HFrEF, HFmrEF, and HFpEF. It should be noted that there was a significant reduction only in HF hospitalization and no reduction in CV death or all-cause death alone and that these results were obtained in a specific population, not already on full doses of HF therapies, who were haemodynamically stable, with elevated NT-proBNP at screening (> 2500pg/mL), and a > 10% decrease in concentration between screening and randomization.

| Variable | | <div><div></div><div>EUVOLEMIA</div><div>CONGESTED</div></div> | | | | |
|----------------------|---|---|---------------|--|--|--|
| Clinical congestion | Orthopnea | None | | Mild | Moderate | Severe/worst |
| | JVP (cm) | <8 and no HJR | <8 | 8-10 or HJR+ | 11-15 | >16 |
| | Hepato megalay | | Absent | Liver edge | Moderate pulsatile enlargement | Massive enlargement and tender |
| | Edema | | None | +1 | +2 | +3/+4 |
| | 6MWT | >400m | 300-400m | 200-300m | 100-200m | <100m |
| Technical evaluation | NP (one of both): -BNP -NT-proBNP | | <100 <400* | 100-299 400-1500 | 300-500 1500-3000 | >500 >3000 |
| | Chest X-ray | clear | clear | cardiomegaly | - pulmonary venous congestion* - small pleural effusions* | - Interstitial or alveolar edema |
| | Vena Cava imaging ⁴⁵ | none of two: - Max diameter >2.2 cm - collapsibility <50% | | One of two: - Max diameter >2.2 cm - collapsibility <50% | | Both: - Max diameter >2.2 cm - collapsibility <50% |
| | Lung Ultrasound ⁴⁴ | <15 B-lines when scanning 28-sites | | 15-30 B-lines when scanning 28-sites | | >30 B-lines when scanning 28-sites |

Figure 2-6: Integrative euvoalaemia/congestion evaluation at discharge. *Chest X-ray can be clear but presence of abnormalities suggests higher degree of congestion. **Source:** Mullens W, Damman K, Harjola VP, et al. The use

Prognosis:

- The in-hospital mortality of acutely decompensated heart failure, whether systolic or diastolic, is ~4%.
- There are four major prognostic risk factors:

- ↑ BUN or creatinine on admission.
- SBP < 115 mmHg.
- “Cold” low-output HF.
- Positive troponin (especially > 1 ng/ml, regardless of the presence of ischemia).

Mortality can go up to 10-20% with one or more of these factors and down to 2% with no factors.

- The mortality and rehospitalization rates at 60 and 90 days are 8-10% and 30%, respectively.
- The mortality and rehospitalization rates at 1 year are 30% and 50%, respectively.

Notes about pharmacological treatment used in treatment of AHF:

1. Diuretics:

Diuretics are a cornerstone in the treatment of patients with AHF and signs of fluid overload and congestion. Diuretics increase renal salt and water excretion and have some vasodilatory effect. In patients with AHF and signs of hypoperfusion, diuretics should be avoided till adequate perfusion.

- **Furosemide dosing:** Loop diuretics are the mainstay of acute HF therapy.

- Bolus: I.V 40-80 mg bolus ⁽¹⁾. I.V 20 mg may be effective in patients who are not receiving chronic furosemide. Doses larger than 80 mg may be needed in renal failure (up to 200 mg single dose).
- Diuretic response should be evaluated shortly after start of diuretic therapy and may be assessed by performing a spot urine sodium content measurement after 2 or 6 h and/or by measuring the hourly urine output. A satisfactory diuretic response can be defined as a urine sodium content > 50-70 mEq/L at 2 h and/or by a urine output > 100-150 mL/h during the first 6 h. The lack of response to dose “X” means that “X” is below a patient-specific threshold dose. Twice the dose “X” should be administered.
- Once the threshold is defined, not much is gained by providing higher single doses, as the maximal response to a single dose is reduced in HF. Frequent dosing of the threshold provides a more effective diuresis and prevents the post-diuretic sodium

(1) A 40 mg intravenous dose of furosemide is approximately equivalent to 80 mg of oral furosemide.

reabsorption that occurs during the diuretic-free intervals. For someone whose diuretic threshold is 40 mg IV, the administration of 40 mg Q6h is better than 80 mg Q12h.

- Alternatively, furosemide may be administered as IV drip when more than 250 mg of IV furosemide is required per day (10-40 mg/hr). A drip may only be started after an effective bolus dose initiates a diuretic response, and each time the drip is up-titrated, the bolus dose is typically administered again.
- **Goal of diuresis:** 2-3 liters of net negative fluid balance per day. The goal is lower in patients who meet the following conditions: **(A)** No significant peripheral edema. **(B)** No LV dilatation (steep pressure-volume relationship). **(C)** Isolated RV failure. **(D)** When the predominant manifestation is ascites ⁽¹⁾.
- **Laboratory monitoring is necessary to detect adverse metabolic effects:**
 - Worsening of renal function. Moderate renal failure is present in 30-64% of acute HF patients on hospital admission. Furthermore, worsening of renal function occurs in ~30% of patients hospitalized with ADHF (worsening= ↑ creatinine by ≥ 0.3 mg/dl).
 - Hypokalemia, Hypomagnesemia, Hypocalcemia.
 - Hypernatremia (the urine induced by loop diuretics is half-tonic, similar to 0.45% half-saline); or hyponatremia from neurohormonal activation.
 - Contraction metabolic alkalosis signals chloride depletion and the need to slow the diuresis or replete the potassium deficit. Diuresis needs to be continued in patients with persistent volume overload, possibly at a slower rate with aggressive potassium replacement.
- **Diuretic resistance:**

Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolaemia. It is seen in up to 25% of ADHF cases.

(1) *The volume clearance across the peritoneal membrane cannot exceed 500ml/day; in patients with predominant ascites, a diuresis of 2 liters per day comes at the expense of the intravascular volume.*

In addition to measuring sodium in a continuous urinary collection, a spot urine sample 1-2 h following loop diuretic administration has demonstrated an excellent correlation with total urine sodium output in a 6 h urine collection.

○ **Several mechanisms are implicated:**

- Reduced renal flow due to high renal afterload (high outflow pressure), and low local cardiac output and low systemic pressure (low inflow pressure).
- Acute, intrinsic kidney injury unresponsive to the diuretic (e.g., ATN).
- Activation of the renin-angiotensin-aldosterone system.
- Hyperfunction of the Henle loop with repeated loop diuretic administration after a first dose (braking phenomenon).
- Post-diuretic rebound effect, i.e., tubular reabsorption of sodium in between doses.
- Hypertrophy of the distal tubules after chronic loop diuretic administration (thiazide benefit), and hyperaldosteronism with exaggeration of the distal sodium retention (spironolactone benefit).

○ **Management:**

- If there is a moderate response to the maximal single dose of furosemide:

Thiazide diuretic may be added to boost the overall, 24-hour urine output. Thiazide diuretics attenuate the distal tubular escape from the loop diuretic effect; thus, they increase the total diuresis but do not initiate diuresis in unresponsive patients. Thiazide is best administered ≥ 1 hr before the loop diuretic, to prevent the distal tubular reabsorption of the sodium released by the loop diuretic. Examples of thiazides include: Oral metolazone 2.5-20 mg Qday ⁽¹⁾, Oral hydrochlorothiazide 25-50 mg Qday, or IV chlorothiazide 500-1000 mg Qday.

Spironolactone may potentiate diuresis in HF, which is a high aldosterone state, but it has a slow onset of action of 2-3 days.

(1) Metolazone is a thiazide-like drug that works on both the proximal and distal tubules and remains effective in advanced renal failure. Metolazone and chlorthalidone have a slow GI absorption (time to peak up to 8 h) and a very long half-life, therefore if low oral doses are started, they should be given hours before the I.V loop diuretic is administered as it will take a long time until a steady state is achieved. However, chlorothiazide has a short half-life so it should be given closer to the loop diuretic.

- Patients who do not achieve appropriate diuresis with a high diuretic dose generally have a very low renal flow; inotropic therapy and/or ultrafiltration may be considered to improve renal perfusion through increasing cardiac output and reducing the renal venous afterload. After 24-48 hrs of inotropic therapy or ultrafiltration, diuretic responsiveness is often restored.
- If no response is achieved with inotropic therapy, acute tubular necrosis is suspected and full hemodialysis rather than ultrafiltration should be used, as ultrafiltration worsens outcomes in advanced renal failure. The following criteria may indicate the need for initiation of renal replacement therapy in patients with refractory volume overload:

Oliguria unresponsive to fluid resuscitation measures.

Severe hyperkalaemia ($K^+ > 6.5$ mmol/L),

Severe acidosis (PH < 7.2)

Serum urea level > 150 mg/dL.

Serum creatinine > 3.4 mg/dL.

N.B: If the patient is still clinically or radiographically congested, continue diuresis even if creatinine rises.

In this case, the rise in creatinine is due to: low output or venous congestion (cardiorenal syndrome) rather than “overdiuresis”, or to a necessary drop of the preload in patients with acute or diastolic HF.

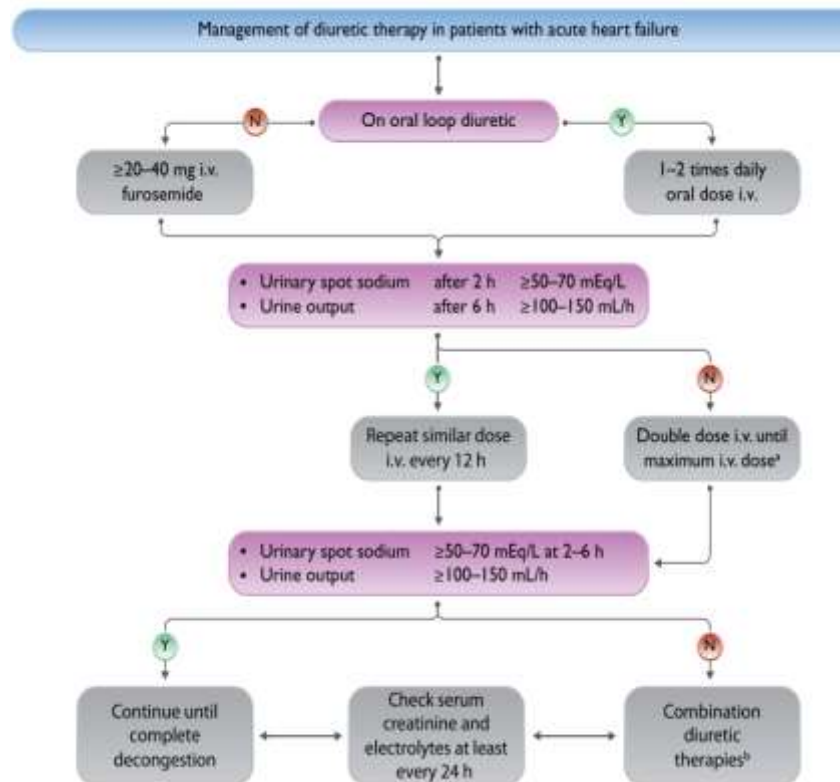


Figure 2-7: Diuretic therapy (furosemide) in acute heart failure. A) The maximal daily dose for i.v. loop diuretics is generally considered furosemide 400–600 mg though up to 1000 mg may be considered in patients with severely impaired kidney function. **B)** Combination therapy is the addition to the loop diuretic of a diuretic with a different site of action, e.g. thiazides or metolazone or acetazolamide. **Source:** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure adopted from Mullens W, et al. (2019)

2. Vasodilators:

- Vasodilators decrease afterload and improve cardiac output; they also have a venodilatory effect that reduces preload, relieves pulmonary edema, and reduces renal afterload. Because of their mechanisms of action, i.v. vasodilators may be more effective than diuretics in those patients whose acute pulmonary oedema is caused by increased afterload and fluid redistribution to the lungs in the absence or with minimal fluid accumulation.
- Vasodilators are only started after ensuring that SBP is stable at > 110 mmHg, rather than maintained by the high catecholamine state of HF (in which case BP may precipitously drop with the relief of dyspnea).
- Vasodilators should be used with caution in patients with significant mitral or aortic stenosis.

- **Intravenous nitroglycerin (NTG):**

Nitroglycerin is a venodilator that acts as a mixed venous and arterial vasodilator at medium doses.

NTG has arterial vasodilatory effects, particularly in the context of severely increased systemic vascular resistance or high-dose diuresis (diuretics activate the RAAS and may lead to vasoconstriction).

Nitrate tolerance develops after several hours of NTG therapy and appears to be improved by the combination with hydralazine or ACE-I.

- **Intravenous nitroprusside:**

Nitroprusside has arterial, venous, and pulmonary vasodilatory properties.

Classically, an arterial line is needed to monitor BP, but this is not always necessary.

Switch to oral vasodilators when stable, such as ACE-Is and/or the combination of hydralazine and oral nitrates, mainly in case of LV systolic dysfunction ⁽¹⁾.

- **Nesiritide:**

(1) A patient who is receiving chronic ACE-I therapy should continue to receive it even if there is some worsening of renal function during the hospital stay, because holding ACE-I may impair outcomes. However, ACE-I should be held acutely in hypotensive, cold HF or severe acute kidney injury. If the patient was not on an ACE-I chronically, avoid starting ACE-I acutely, in the first few hours, before making sure the patient is hemodynamically stable. The combination of hydralazine and nitrates can be started acutely in HF.

Nesiritide is a recombinant form of BNP that is administered intravenously. It is a potent venous and arterial vasodilator with a mild direct diuretic effect. It enhances sodium and water excretion and has been shown to reduce PCWP as well as BP. This agent has not been shown to improve survival.

The duration of action of nesiritide is 3 hours, i.e., longer than NTG and nitroprusside.

If hypotension occurs, this prolonged effect increases the chances of renal failure and mortality. This hypotension is potentially more harmful than the hypotension seen with other IV vasodilators.

Thus, nesiritide has an unclear role and should be avoided if SBP < 110 mmHg.

- **Serelaxin (investigational):**

Serelaxin, an intravenous vasodilator, is a recombinant form of relaxin, the natural hormone that promotes vasodilatation in pregnancy.

In the RELAX-HF trial of ADHF patients with SBP > 125 mmHg, the use of serelaxin for 2 days on top of diuretic therapy was associated with improved dyspnea, improved mortality at 60 days, and an early improvement of biomarkers (troponin, renal function, BNP).

| Table 2-5: Intravenous vasodilators used to treat AHF: | | | |
|--|---|--|------------------------------|
| Vasodilator | Mechanism of action | Dosing | Side effects |
| Nitroglycerin | <i>Enters vascular smooth muscle and is converted to NO → ↑ intracellular cGMP → vascular smooth muscle relaxation. (dose-dependant dilation of arteries and veins)</i> | <i>Start with 10-20 µg/min ⁽¹⁾, increase up to 200 µg/min</i> | <i>Hypotension, headache</i> |
| Isosorbide dinitrate | | <i>Start with 1 mg/h, increase up to 10 mg/hr.</i> | |

(1) Nitroglycerine can be given as 1-2 mg boluses in severely hypertensive patients with acute pulmonary oedema.

| | | | |
|----------------------|---|---|---|
| Nitroprusside | <i>Produce NO → ↑ intracellular cGMP → Ca movement from cytoplasm to endoplasmic reticulum → vascular smooth muscle relaxation.</i> | <i>Start with 0.3 µg/kg/min and increase up to 5 µg/kg/min.</i> | <i>Hypotension, isocyanate toxicity</i> |
| Nesiritide | <i>Recombinant form of BNP → ↑ intracellular cGMP → vascular smooth muscle relaxation → Vasodilatation with mild diuretic effect.</i> | <i>Bolus 2 µg/kg + infusion 0.01 µg/kg/min.</i> | <i>Hypotension</i> |

3. Inotropes/Vasopressors:

- IV inotropic agents may worsen survival over the long-term even when used temporarily; therefore, they should be avoided if possible. An inotrope, typically dobutamine, is still indicated temporarily in wet and cold HF with SBP < 85-90 mmHg **or** not responding to diuresis.
- Inotropes can often be weaned off within a few days. Inotropes initiate diuresis and reduce ventricular volumes, and thus improve ventricular afterload, functional MR/TR, and myocardial perfusion in a sustained fashion. This allows the patient to tolerate inotrope discontinuation and tolerate lower systemic pressures without compromise of myocardial perfusion. Also, renal function improves enough to allow the sustainment of diuresis.
- In patients with less severe HF, aggressive diuresis achieves a similar sustained benefit to inotropes.
- **Dobutamine:**
- **Mechanism of action:** Dobutamine has marked β_1 -agonist, and less marked β_2 - and α_1 -agonist effect.

The β_2 - and α_1 -receptors have counter effects on the vasculature (vasodilatation and vasoconstriction, respectively), which explains that the vasodilatory and hypotensive effects of dobutamine are usually mild, and in fact BP often improves with the increase in cardiac output.

Only in critical patients with severe vasoconstriction and occupancy of all α -receptors, dobutamine may have a predominant β_2 and vasodilatory effect.

- **Dose:** A low dose of dobutamine (2-5 mcg/kg/min) usually provides the desired effect. Higher doses (up to 20 mcg/kg/min) may be required in patients previously receiving β -blockers.

- **Milrinone:**

- **Mechanism of action:** Milrinone is a phosphodiesterase-3 inhibitor that increases intracellular cAMP along the β -receptor pathway. It has more marked vasodilatory and hypotensive effects → ↓ afterload.

- **Dose: Bolus:** 25-75 μ g/kg over 10–20 min .. **Maintenance:** 0.375-0.75 μ g/kg/min.

Start a small drip of milrinone (0.2 mcg/kg/min) and titrate it very slowly every few hours, allowing the increase in cardiac output to catch the vasodilatory effect, therefore preventing hypotension.

- Milrinone has more prolonged effect than dobutamine, with a 2.5-hour half-life, more so in renal failure. The dose should be reduced by 50% in renal failure.
- Milrinone should be avoided if SBP < 80 mmHg, particularly the bolus dose which is better to be avoided.
- Milrinone has significant pulmonary vasodilatory potential and may be the preferred inotrope in patients with pulmonary hypertension.
- The most common arrhythmia with milrinone is AF (up to 25%), while the most common arrhythmia with dobutamine is sinus tachycardia. Asymptomatic PVCs are common with both, more so dobutamine, but VT is rare.

- **Levosimendan:**

- **Mechanism of action:**

- Increase myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent manner → increasing cardiac contractility without a rise in intracellular calcium.

- Open of ATP-sensitive potassium channels → vasodilation.
- **Dose: Bolus:** 12 µg/kg over 10 min (optional) .. **Maintenance:** 0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min.
- It is a vasodilator, thus it is not suitable for treatment of patients with hypotension (SBP < 85 mmHg) or cardiogenic shock unless in combination with other inotropes or vasopressors.
- **Dopamine:**
 - **Mechanism of action:** Endogenous catecholamine, acting on both dopaminergic and adrenergic neurons.
 - Low dose (3-5 µg/kg/min.) stimulates dopaminergic receptors → renal and mesenteric vasodilation.
 - Higher dose (5-10 µg/kg/min) stimulates both beta1- and dopaminergic receptors, → cardiac stimulation and renal vasodilation.
 - Large dose (> 10 µg/kg/min) stimulates alpha-adrenergic receptors.
 - For a similar increase in cardiac output, dopamine produces greater elevation in heart rate and more arrhythmias than dobutamine and norepinephrine.
- **Norepinephrine**
 - **Mechanism of action:** have inotropic and vasoconstrictive effects.
 - Stimulates α1 and α2 receptors → Vasoconstriction → increases peripheral vascular resistance.
 - Acts on beta-1 adrenergic receptors → ↑ heart rate and cardiac output.
 - **Dose:** 0.2-1.0 µg/kg/min
- **Epinephrine (adrenaline):**
 - **Mechanism of action:** have inotropic and vasoconstrictive effects.
 - Stimulates α1 and α2 receptors → Vasoconstriction → increases peripheral vascular resistance.
 - Acts on beta-1 adrenergic receptors → ↑ heart rate and cardiac output.
 - **Dose:** 0.05-0.5 µg/kg/min

- It should be restricted to patients with persistent hypotension despite adequate cardiac filling pressures and the use of other vasoactive agents, as well as for resuscitation protocols.

N.B:

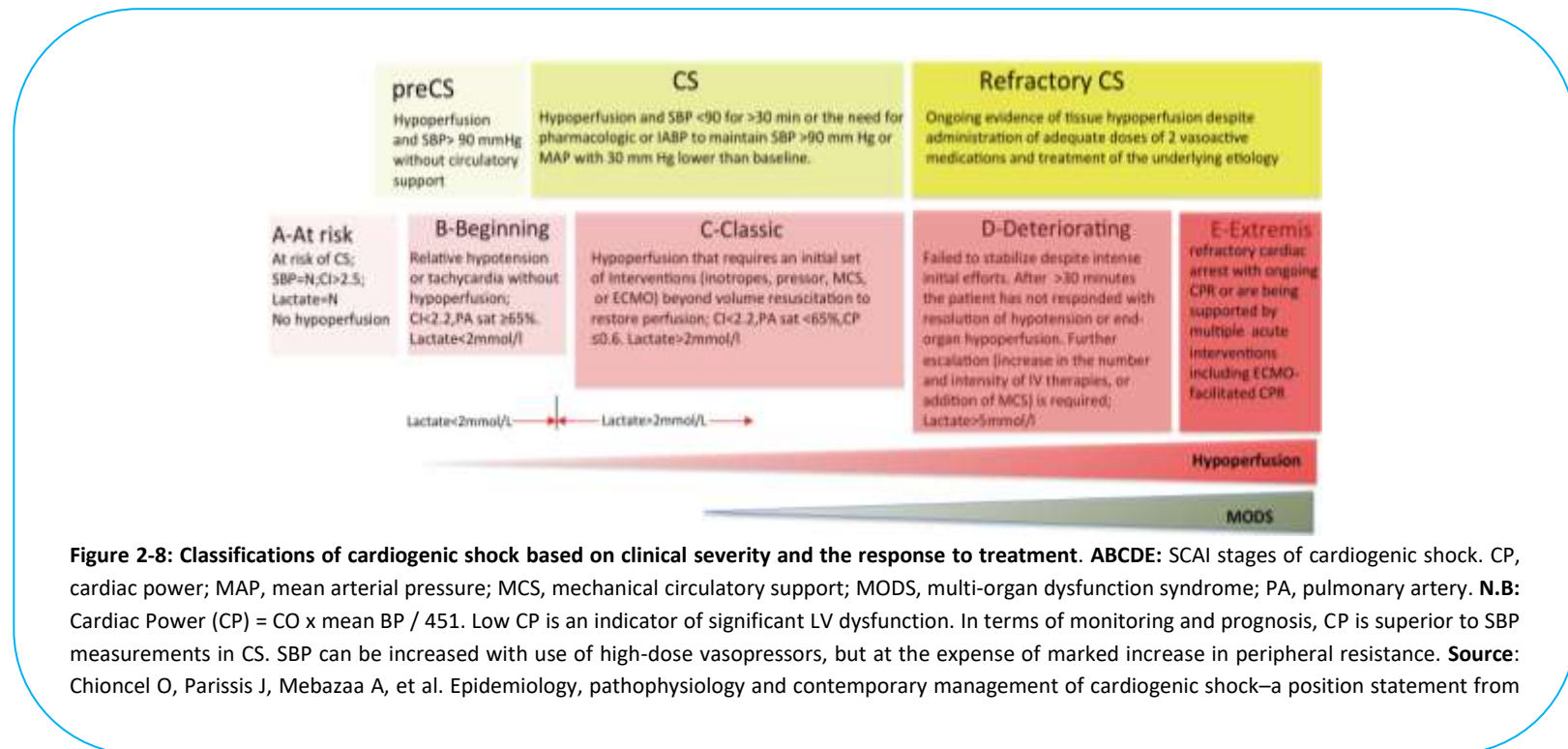
- ☞ The routine use of a Swan-Ganz catheter (PA catheter) in acute HF does not improve outcomes. It is used selectively to monitor RA pressure, pulmonary capillary pressure, and cardiac output, if:
 - The patient's BP or respiratory status does not improve after initiation of medical treatment and the volume status is unclear.
 - There is progressive renal failure with diuretic resistance.
 - A mixed shock is suspected (cardiogenic and septic).
 - There is uncertainty about the diagnosis of cardiogenic shock, especially in the "cold dry" subgroup.
- ☞ Beta-blockers can be safely **continued** during AHF presentations except in cardiogenic shock. A recent meta-analysis demonstrated that discontinuation of beta-blockers in patients hospitalized with AHF was associated with significantly increased in-hospital mortality, short term mortality and the combined endpoint of short-term rehospitalization or mortality.
- ☞ Levosimendan or type-3-phosphodiesterase inhibitors may be preferred over dobutamine for patients on beta-blockers as they act through independent mechanisms.
- ☞ LV perfusion is mainly diastolic and depends on the gradient between aortic DBP and LVEDP. RV perfusion is diastolic and systolic and depends on the gradient between aortic DBP and RVEDP, as well as the gradient between aortic SBP and RV systolic pressure. A reduction in LVEDP improves LV perfusion, while a reduction in RVEDP and RV systolic pressure, i.e., PA pressure, improves RV perfusion.

Cardiogenic shock (CS)

- **Definition and prognosis:**

Cardiogenic shock is a syndrome due to primary cardiac dysfunction resulting in an inadequate cardiac output, comprising a life-threatening state of tissue hypoperfusion ⁽¹⁾, which can result in multiorgan failure and death. CS accounts for 2-5% of AHF presentations, with in-hospital mortality between 30-50%, with nearly half of in-hospital deaths occurring within the first 24 h of presentation.

- **Classification:**



(1) Of note, hypoperfusion is not always accompanied by hypotension, as BP may be preserved by compensatory vasoconstriction (with/without pressor agents), albeit at the cost of impaired tissue perfusion and oxygenation.

- Pathophysiology:

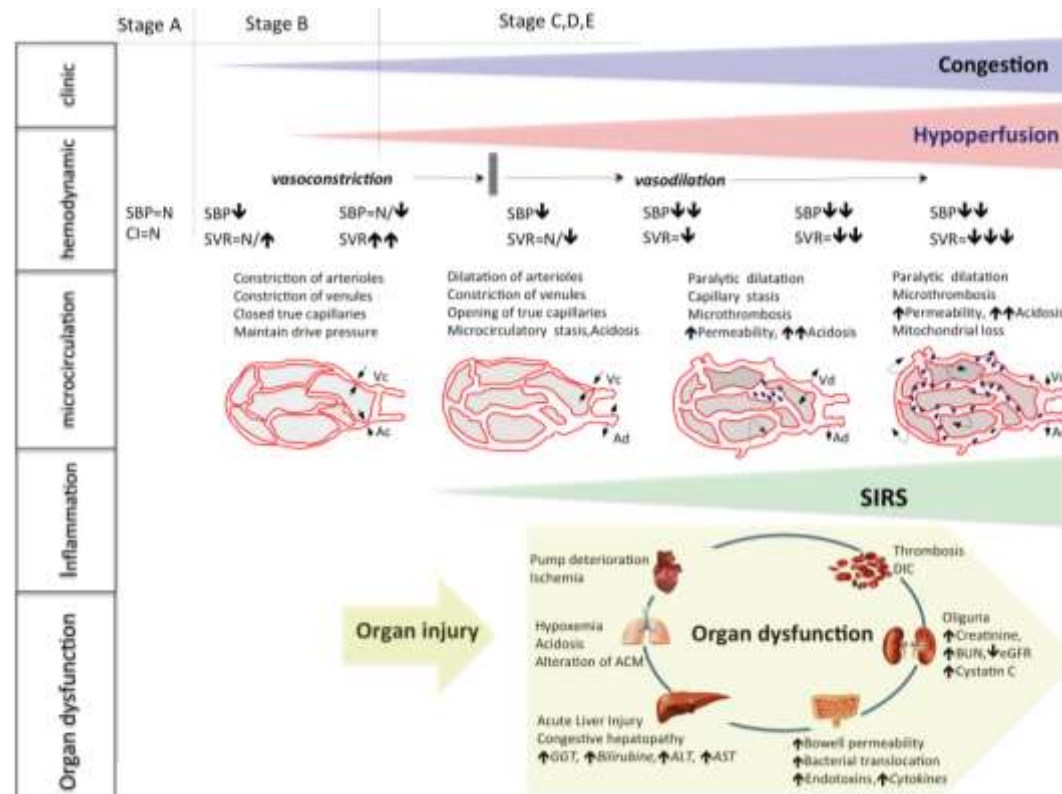


Figure 2-9: Pathophysiology of cardiogenic shock with staged abnormalities. On the upper row, the SCAI classification is presented. Ac, arteriolar constriction; Ad, arteriolar dilatation; ACM, alveolar-capillary membrane; GGT, gamma glutamyltransferase; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TMAO, trimethylamine N-oxide; Vc, venous constriction; Vd, venous dilatation. **Source:** Chioncel O, Parissis J, Mebazaa A, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock—a position statement from the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2020 Aug;22(8):1315-41

- Monitoring and investigations:

- Immediate assessment of hypoperfusion signs and continuous monitoring of SBP, rhythm, respiratory rate and saturation is recommended.
- A 12-lead ECG should be immediately performed followed by continuous ECG monitoring.
- Echocardiography should be performed urgently to determine the underlying diagnosis, guide interventions and monitor response to therapies.
- Chest X-ray for the evaluation of congestion and to monitor the catheter and cardiac device position.
- Biomarkers: Elevated lactate reflects inadequate tissue oxygenation/metabolism, and the diagnosis of shock includes serum lactate > 2 mmol/L, which also has a strong prognostic role ⁽¹⁾. Natriuretic peptides are markers of disease severity and indicative of increased filling pressures.
- Insertion of an arterial line and central venous catheter is recommended in all CS patients.
- PA catheter may be considered in selected patients who failed to respond to initial therapeutic interventions, or in case of diagnostic/therapeutic uncertainty (e.g., cases of mixed shock).

● **Management of LV-related cardiogenic shock:**

- **Mechanical ventilation:** Acute respiratory failure is present in almost all patients presenting with CS. Hypoxaemia and hypercapnia are the consequences of intrapulmonary shunting generated by pulmonary congestion and the reduction in lung space with increasing ventilation-perfusion mismatch. In addition, lactic acidosis increases the compensatory respiratory load with hyperventilation, thereby augmenting total body oxygen requirements. No specific ventilation modality has demonstrated superiority over the others. However, high PEEP is poorly tolerated, particularly in RV dysfunction.
- **In ACS-related cardiogenic shock:**
 - **Emergent revascularization:** Culprit lesion-only PCI is recommended as the default strategy in patients with AMI with cardiogenic shock (CULPRIT-SHOCK trial).

(1) Potential causes of lactate elevations (e.g., DKA, liver insufficiency, trauma, epinephrine, propofol, linezolid) should be considered when lactate level is dissociated to hypoperfusion status.

Note that, In cardiogenic shock, enteral antiplatelet administration may be inconsistent because of poor splanchnic perfusion and absorption and decreased hepatic bioactivation of thienopyridine (more in cases of therapeutic hypothermia after cardiac arrest). Cangrelor infusion provides rapid onset of action because its bioavailability does not depend on hepatic and GI perfusion.

- **IABP** may be placed during or before the revascularization procedure to stabilize the patient, reduce O₂ demands, and perform a safer PCI with a potential for less reperfusion injury.
- **Fluid challenge:** Almost one third of patients presenting with CS are ‘euvolaemic’, but respond to fluid administration by increasing stroke volume. Fluid challenge with normal saline or Ringer’s lactate (250 mL over 15-30 min) should be considered as first-line treatment, if there are no signs of congestion.
- **Inotropic support:**
 - Dobutamine or dopamine is used in patients whose SBP is > 70 mmHg, while norepinephrine is required in patients with SBP < 70 mmHg or inappropriately low or normal SVR. While vasoconstriction may be harmful, the maintenance of an appropriate systemic perfusion pressure, including coronary perfusion pressure, is a priority and justifies the use of norepinephrine in severely hypotensive patients.
 - Levosimendan may be used in CS patients already on chronic beta-blocker therapy, as well as in patients with CS and acute RV failure or pulmonary hypertension, owing to its favourable effects on PVR.
- **LV assist device**, such as percutaneous Impella or TandemHeart, may be considered in patients with cardiogenic shock refractory to inotropes/vasopressors as it provides better support than IABP.
- **Temporary pacing**, usually at a rate over 80-100 bpm, is required if the heart rate is inappropriately low or even “normal” (60-70 bpm).

Table 2-6: ESC Recommendations for the management of patients with cardiogenic shock:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Emergency coronary angiography is indicated in patients with acute heart failure or cardiogenic shock complicating ACS.</i> | I | B |

| | | |
|--|------------|----------|
| <i>Emergency PCI of the culprit lesion is indicated for patients with cardiogenic shock due to STEMI or NSTEMI-ACS, independent of time delay of symptom onset, if coronary anatomy is amenable to PCI.</i> | I | B |
| <i>Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.</i> | I | B |
| <i>In cases of hemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is indicated, as decided by the Heart Team.</i> | I | C |
| <i>In selected patients with ACS and cardiogenic shock, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.</i> | IIb | C |
| <i>Routine use of IABPs in patients with cardiogenic shock due to ACS is not recommended.</i> | III | B |

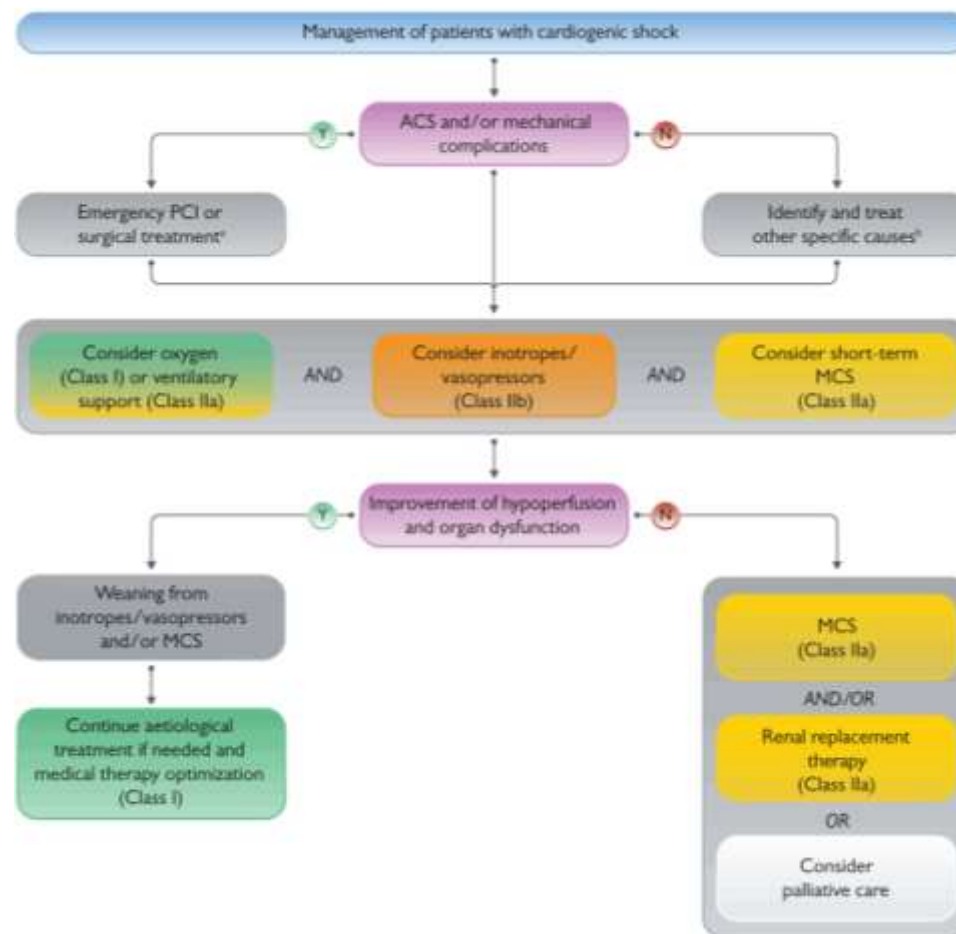


Figure 2-10: Management of cardiogenic shock. MCS= mechanical circulatory support. **A)** PCI in ACS, pericardiocentesis in tamponade, mitral valve surgery in papillary muscle rupture. In case of interventricular septum rupture, MCS should be considered. **B)** Other causes include acute valve regurgitation, pulmonary embolism, infection, acute myocarditis, arrhythmia. **Source:** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

Isolated or Predominant RV failure

Acute RV failure can be defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output. Acute pulmonary hypertension is at the center of most cases of acute RV failure.

- **Causes of right sided HF:**

1. Pressure overload:

- Acute pulmonary hypertension e.g pulmonary embolism, acute lung injury or ARDS.
- Chronic pulmonary hypertension (groups 1–5)

2. Volume overload (e.g., tricuspid valve regurgitation, ASD).

3. Intrinsic RV disease (e.g., ischemia, cardiomyopathy, congenital heart disease or arrhythmia)

- **RV morphological features:**

As opposed to the LV, which has an elliptical shape, the RV has the shape of a pyramid connected to an infundibular tube. In contrast to the LV, twisting and rotational movements do not contribute significantly to RV contraction. Instead, the most important mechanisms are the bellows-like inward movement of the free wall, the contraction of the longitudinal fibres drawing the tricuspid annulus toward the apex, and the traction on the free wall as a result of LV contraction.

The contraction of the RV is sequential, starting with the trabeculated myocardium and ending with the contraction of the infundibulum (25-50 ms delay).

- **Pathophysiology:** RV function integrates preload, afterload, contractility, pericardial constraint, interaction with the LV, and cardiac rhythm. RV Failure may result from pressure overload or volume overload or primary reduction of myocardial contractility (e.g ischaemia, cardiomyopathy, or arrhythmia).

- **Afterload sensitivity:**

As opposed to the normal LV, the RV poorly tolerates acute afterload changes and is more likely to fail from acute pressure overload (e.g pulmonary embolism) than from volume overload (e.g ASD, primary TR). This is due to the fact that the RV wall is

thinner than the LV wall, afterload inversely correlating with myocardial thickness (Laplace law: Wall stress or Afterload = Pressure × Radius / [2 × wall thickness]) ⁽¹⁾.

As the RV severely fails and dilates, progressive RV dilatation leads to progressively more wall stress on the thin walls, which leads to further RV dilatation (vicious circle). The pericardium is helpful in those cases as it tries to contain the RV; pericardiotomy/cardiac surgery may lead to massive RV dilatation.

○ **Ventricular interdependence:**

Ventricular interdependence relates to the concept that the functioning of the LV affects the functioning of the RV and vice versa. The main anatomical determinants of ventricular interdependence include the interventricular septum, the pericardium, and the continuity between myocardial fibres of the LV and RV.

LV failure leads to RV failure through pulmonary hypertension and through the loss of septal contribution to RV function. In fact, the septum and the RV free wall contribute almost equally to the RV function, and 20-40% of RV systolic pressure and output result from LV contraction.

On the other hand, RV failure, particularly when acute, may lead to LV failure. When the RV dilates acutely, the interventricular septum is shifted leftward, both in systole and diastole as both ventricles 'compete' for space within the pericardium. Septal shift compresses the LV, impairs its filling, and leads to reduced LV contractility.

N.B:

- ☞ As opposed to the adult RV, the thick congenital RV tolerates pressure overload and does not fail (e.g., pulmonic stenosis, Eisenmenger syndrome).
- ☞ Severe RV failure may lead to refractory hypoxemia. The high RA pressure may induce a large right-to-left shunting in patients with PFO.

(1) *The RV is not built to handle rapid increases in PA pressure. However, it possesses the capacity to adapt its systolic function to preserve ventriculo-arterial coupling. During the acute response, the RV uses a homeometric or systolic functional adaptation (Anrep's law of the heart) within minutes of a rise in PA pressure; chronically it implements a heterometric or dimensional adaptation (Starling's law of the heart) to preserve flow output.*

☞ In patients with severe pulmonary hypertension, the PA pressure may decline into the mild/moderate range as RV failure develops. In those patients, a high systolic PA pressure predicts recovery of RV function with therapy and better outcomes than lower systolic PA pressure.

- **Echocardiographic features of RV dysfunction:**

While the RV diameter is smaller than the LV diameter on the apical four-chamber view, the three-dimensional RV volume is actually larger than the LV volume, which implies that normally the RV EF is lower than LV EF, with 40% as the lower limit of normal ($EF = \text{stroke volume} / \text{ventricular diastolic volume}$; for the same stroke volume, the ventricular volume is larger on the right).

RV volume and EF are better assessed by 3D echocardiography MRI or first-pass nuclear scan.

RV septal motion should be analyzed for RV volume overload (septum pushed towards the LV in diastole, with paradoxical motion in systole), and RV pressure overload (septum pushed towards the LV in systole, called D-shaped septum).

Two echo indices are valuable for the assessment of RV systolic function:

1. TAPSE (normal > 16 mm), which is the systolic excursion of the lateral tricuspid annulus toward the apex, measured on M mode.
2. Tissue Doppler of the lateral tricuspid annulus (called S', normal > 10 cm/s).

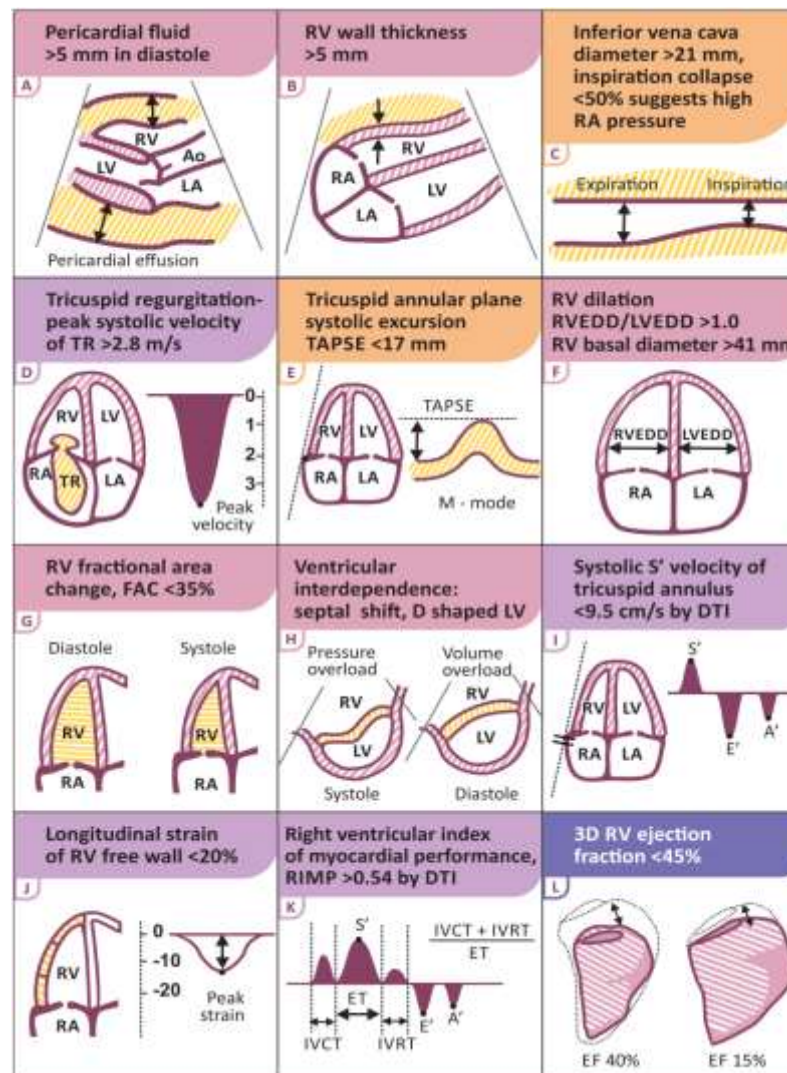


Figure 2-11: Graphic representation of echocardiographic parameters in the assessment of RV failure. Source: Harjola VP, Mebazaa A, Čelutkienė J, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. European journal of heart failure. 2016 Mar;18(3):226-41.

- **Diagnosis of the underlying mechanism of RV failure:**

Pressure overload **vs.** Volume overload **vs.** Intrinsic RV disease.

- **PA pressure > 50, or PVR ↑:** Pulmonary hypertension, possibly from left HF.

PA pressure may be normal if cardiac output is poor (severe RV failure), but PVR unveils the diagnosis of pulmonary hypertension.

- **PA pressure normal or < 50, and PVR normal:**

Isolated right HF from volume overload (ASD, TR), or intrinsic RV disease (cardiomyopathy, RV MI).

- **Treatment of acute, isolated, or predominant RV failure:**

- **Underlying causes of RV failure should be treated.** Respiratory failure with hypoxemia, often a major culprit of acute RV failure, should be aggressively treated, with mechanical ventilation if needed.

- **Preload management:**

- In chronic RV failure, mild progressive diuresis is beneficial to reduce RV dilatation, improve RV function, improve functional TR, and reduce ventricular interdependence, all of which improve cardiac output. Unless left-sided volume overload is also present, aggressive diuresis (> 1 L/day) is avoided, as it may worsen the underfilling of the already small LV cavity.

- In cases of acute RV failure secondary to RV MI or PE, volume loading is justified as the RV increases its stroke volume with increasing preload, before reaching the point of ventricular interdependence. Note that, high CVP does not imply a high preload in acute, de novo, RV failure.

- **Vasopressor and inotrope treatment:** If there is no hemodynamic response to fluid, stop volume loading to avoid further RV dilatation, and *consider inotropes/vasopressors*. Noradrenaline is primarily indicated to restore blood pressure and improve coronary and organ perfusion without change in PVR. Dobutamine, levosimendan and milrinone improve contractility and increase cardiac output. Note that digoxin may also be useful in RV failure.

- **Afterload reduction (PVR):** Hypoxia and hypercapnia, as well as acidosis and hypothermia, promote pulmonary vasoconstriction and further increase the RV afterload. Treatment of hypoxemia is key.

Epoprostenol is the only PAH-specific drug that has been shown to improve survival in WHO functional class IV PAH patients. Nitric oxide is frequently used in post cardiac surgery patients. It seems especially promising in patients having right ventricular failure after orthotopic heart transplant.

- **Maintain sinus rhythm and AV synchrony:**

- AF **or** AV dissociation may have more profound hemodynamic effects in RV failure than LV failure.

- **AF:** In RV failure, the LV is compressed, and underfilled, which makes it highly dependent on the atrial kick. LA contraction is a major contributor to LV filling and LV output in RV failure (more than in LV failure). RA contraction directly raises RV pressure and, thus, flow into the PA. *So, consider prompt DC cardioversion in AF associated with acute RV shock, even if the rate is reasonably controlled.*

- **AV block:** In RV shock associated with AV block, AV synchronous pacing should be performed (temporary atrial and ventricular leads are placed through two separate venous accesses). An increase in heart rate (80-120 bpm) is necessary to allow RV filling and emptying through providing more cardiac cycles.

- **Mechanical circulatory support** of the RV (e.g., ECMO or RVADs) may be required in certain situations such as RV infarction, acute PE, following LVAD implantation, or primary graft failure after heart transplantation.

- **Heart transplant** remains the ultimate treatment for refractory RV failure.

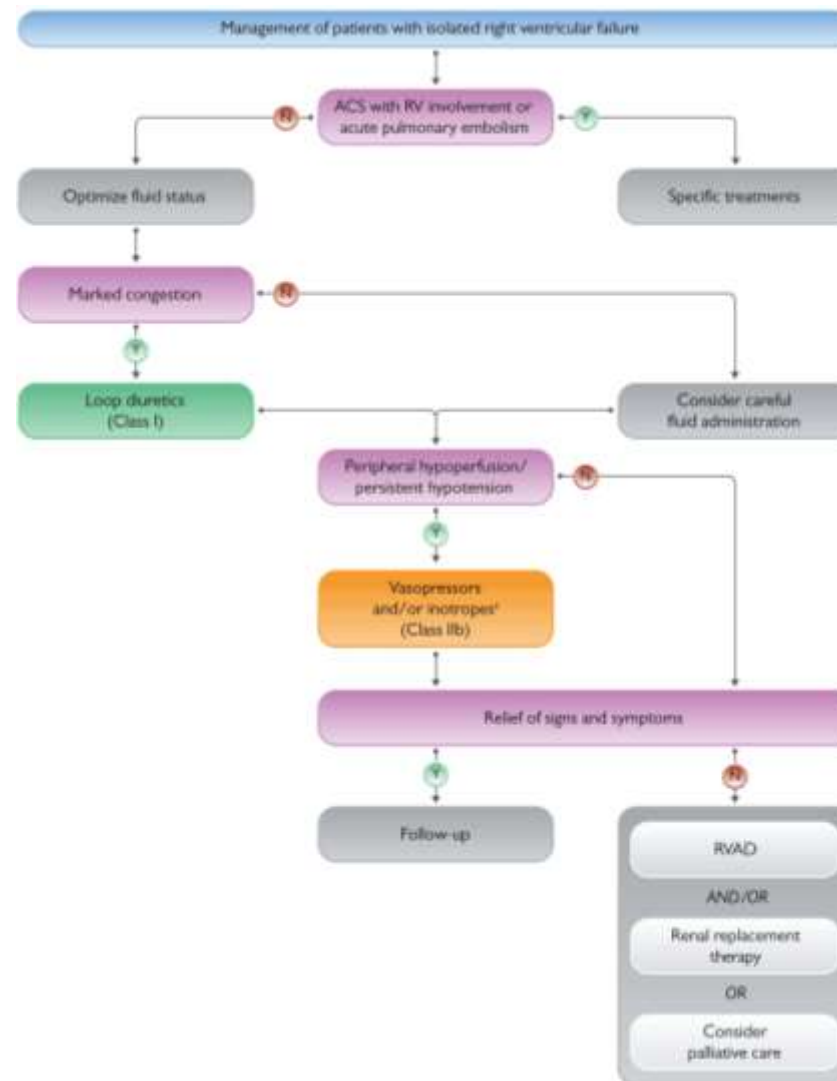


Figure 2-12: Management of right ventricular failure. A) Inotropes alone in case of hypoperfusion without hypotension. **Source:** 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

Tips in management of RV failure:

- ☞ **Effect of mechanical ventilation in RV failure:** Mechanical ventilation reduces hypoxia, and thus improves PVR and RV output. However, positive-pressure ventilation with a high pressure or volume compresses the alveolar capillaries and increases RV afterload and further decreases LV preload, while a very low volume ventilation leads to atelectasis and arterial compression. *A strategy of low tidal volume with limited plateau pressure should be implemented.*
- ☞ **Effect of Right-to-left shunting through a PFO:** Right-to-left shunting through a PFO serves to unload the RV, reduce RA pressure, and increase the LV filling and cardiac output. Thus, although this shunt induces hypoxemia (SaO_2 80-85%), some degree of shunting improves the cardiac output, the overall oxygen delivery, and the patient's symptoms and functional status and should not be closed. In fact, patients with Eisenmenger syndrome and patients with PAH who have a PFO live longer than patients with no shunt. *That is why balloon atrial septostomy has been beneficial in cases of refractory right HF.* Only excessive shunting, as in patients with very high RA pressure > 20 mmHg and very poor RV function, may drastically reduce pulmonary blood flow and induce severe hypoxemia (overall untoward effect).
- ☞ **Effect of hypotension in RV failure:** As opposed to the failing LV, the failing RV is less tolerant of a low SBP. In LV failure, a low SBP reduces afterload and may significantly increase cardiac output. The RV, on the other hand, depends on an adequate SBP for its coronary perfusion. While the LV coronary flow is mostly diastolic, the RV coronary flow is at least 50% systolic, and depends on the gradient between SBP and systolic RV pressure. If the SBP is low in a patient with a high PA pressure, the gradient between SBP and systolic RV pressure is reduced, which reduces RV coronary flow leading to RV ischemia and failure.
- ☞ **Effect of vasodilation in RV failure:** Systemic vasodilators are poorly tolerated in RV failure because the underfilled LV cannot increase its output to match the vasodilated circulation. Dobutamine and milrinone increase RV contractility and reduce PVR; however, they are also systemic vasodilators and thus must be used in conjunction with vasopressors, such as norepinephrine or vasopressin.
- ☞ **In RV infarction:** the RV tolerates ischaemic injury better than the LV because it has a lower oxygen demand, greater oxygen extraction reserve capability during stress, dual anatomical supply from the right and left coronary arteries, relatively homogeneous transmural perfusion across the cardiac cycle, and increased propensity to acute collateral development. Unlike

the LV, the RV may remain viable for days after an infarct. Therefore, late reperfusion is an option that may be considered in patients with inferior MI complicated by RV dysfunction.

☞ **RV dysfunction after cardiac surgery:** In cardiac surgery, RV function can be jeopardized by several factors, such as suboptimal myocardial protection, myocardial stunning after long durations on cardiopulmonary bypass, air embolism to the RCA, and mechanical occlusion or kinking of the right coronary button or bypass graft.

Combined antegrade and retrograde cardioplegia provide superior RV myocardial protection. Avoiding cardiopulmonary bypass may theoretically improve RV myocardial protection, although no differences were observed in long-term follow-up. Liberal transfusion strategies should be avoided to prevent increased RV load and negative outcomes. Occasionally, patients may not tolerate sternal closure after cardiac surgery; delayed sternal closure for 24 h or more may reduce extrinsic RV compression.

☞ Pulmonary artery pulsatility index = $(\text{Systolic PAP} - \text{diastolic PAP}) / \text{CVP}$.

It is a novel hemodynamic index that predicts severe RVF. If < 0.9 , indicates significant RV failure.

Important trials in acute heart failure:

| Table 2-7: Clinical trials of Acute Heart failure: | |
|--|--|
| Trial (date) | Summary |
| Pulmonary artery catheter: | |
| ESCAPE (2005) | <p>Aim: To assess the safety and efficacy of pulmonary artery catheter (PAC) in patients hospitalized with severe symptomatic and recurrent heart failure.</p> <p>Study: 433 patients hospitalized with severe symptomatic and recurrent HF were assigned to receive therapy guided by clinical assessment and PAC or clinical assessment alone. The target in both groups was resolution of clinical congestion, with additional PAC targets (PCWP of 15 mmHg and RAP of 8 mmHg). Medications were not specified, but inotrope use was explicitly discouraged. Addition of the PAC to careful clinical assessment increased anticipated adverse events, but did not affect overall mortality and hospitalization.</p> |
| Continuation of B-blockers: | |
| B-CONVINCE D (2009) | <p>Aim: To assess whether beta-blocker therapy should be stopped during acutely decompensated heart failure (ADHF).</p> <p>Study: 147 patients with LVEF < 40% admitted with ADHF previously receiving stable beta-blocker therapy were assigned to either continuation or discontinuation of beta-blockers. Continuation of beta-blocker therapy is not associated with delayed or lesser improvement, but with a higher rate of chronic prescription of beta-blocker therapy after 3 months, the benefit of which is well established.</p> |
| SGLT2-inhibitors: | |
| SOLOIST-WHF (2021) | <p>Aim: To assess sotagliflozin would reduce the risks of CV mortality, HF hospitalization, and an urgent visit for HF among patients with DM and recent worsening of HF when administered soon after an episode of decompensated HF.</p> <p>Study: 1222 patients with type 2 DM recently hospitalized for worsening HF were randomly assigned to receive sotagliflozin or placebo. The primary endpoint was CV deaths and hospitalizations and urgent visits for HF. The trial</p> |

| | |
|--------------------------|---|
| | <i>ended early because of loss of funding. Sotagliflozin, initiated before or shortly after discharge, resulted in a significantly lower total number of CV deaths and hospitalizations and urgent visits for HF than placebo.</i> |
| EMPULSE (2022) | <p>Aim: <i>To evaluate the effects of empagliflozin on decongestion-related endpoints and explore if decongestion itself translates into clinical benefit.</i></p> <p>Study: <i>530 patients hospitalized for AHF were randomized 1:1 to either empagliflozin 10 mg once daily or placebo for 90 days. The outcomes investigated were: weight loss (WL), WL adjusted for mean daily loop diuretic dose (WL-adjusted), area under the curve of change from baseline in NT- pro-BNP levels, hemoconcentration, and clinical congestion score after 15, 30, and 90 days of treatment. Initiation of empagliflozin in patients hospitalized for AHF resulted in an early, effective and sustained decongestion which was associated with clinical benefit at Day 90.</i></p> |
| ARNI: | |
| PIONEER-HF (2018) | <p>Aim: <i>To evaluate the use of sacubitril/valsartan, as compared with enalapril, in the treatment of patients who were hospitalized for acute HF.</i></p> <p>Study: <i>881 patients with HFrEF who were hospitalized for acute decompensated heart failure were randomly assigned to receive sacubitril-valsartan (97/103 mg twice daily) or enalapril (10 mg twice daily) after hemodynamic stabilization. The primary efficacy outcome was the proportional change in the NT-proBNP from baseline through weeks 4 and 8. Sacubitril-valsartan led to a greater reduction in the NT-proBNP concentration than enalapril.</i></p> |
| Iron replacement: | |
| AFFIRM-AHF (2020) | <p>Aim: <i>To evaluate i.v ferric carboxymaltose (IV FCM) among patients hospitalized for acute heart failure and iron deficiency compared with placebo.</i></p> <p>Study: <i>1132 eligible patients hospitalized with acute HF were randomly assigned to receive either IV FCM or placebo. The primary outcome, total heart failure hospitalizations and CV death within 52 weeks. IV FCM was associated with a numerical reduction in total HF hospitalizations and CV death.</i></p> |
| Diuretics: | |

| | |
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| DOSE (2011) | <p>Aim: To evaluate the safety and efficacy of two strategies for furosemide dosing in patients with ADHF: (1) route of administration (Q12 hour bolus vs. continuous infusion), and (2) dosing (low intensification to 1x oral dose vs. high intensification to 2.5x oral dose).</p> <p>Study: 308 patients with acute decompensated heart failure were randomly assigned to receive i.v furosemide administered either a bolus every 12 hrs or continuous infusion and at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). Among patients with ADHF, there were no significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose.</p> |
| ADVOR (2022) | <p>Aim: To assess whether acetazolamide can improve the efficiency of loop diuretics in patients with acute decompensated HF with volume overload.</p> <p>Study: 519 patients with acute decompensated HF, clinical signs of volume overload (i.e., edema, pleural effusion, or ascites), and an NT-pro-BNP > 1000 pg/ml or BNP > 250 pg/ml were randomly assigned to receive either i.v acetazolamide (500 mg once daily) or placebo added to standardized i.v loop diuretics. The primary endpoint was successful decongestion within 3 days after randomization and without an indication for escalation of decongestive therapy. Addition of acetazolamide to loop diuretics resulted in a greater incidence of successful decongestion in patients with acute HF.</p> |
| CLOTOTIC (2023) | <p>Aim: To evaluate the safety and efficacy of the addition of hydrochlorothiazide to i.v furosemide for improving diuretic response in acute HF.</p> <p>Study: 230 adult patients with AHF (had a history of chronic HF and had been hospitalized within the previous 24 h for acute decompensated HF who were treated with oral loop diuretic, for at least 1 month before hospitalization) were randomized to receive HCTZ or placebo in addition to an intravenous furosemide regimen. The coprimary endpoints were changes in body weight and patient-reported dyspnoea 72 h after randomization. The addition of HCTZ to loop diuretic therapy improved diuretic response in patients with AHF.</p> |

Ultrafiltration:

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| CARRESS-HF (2012) | <p>Aim: <i>To assess the effect of ultrafiltration on renal function and weight loss in patients with HF and worsening renal function and persistent congestion.</i></p> <p>Study: <i>188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy or ultrafiltration. The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days. The use of a stepped pharmacologic-therapy algorithm was superior to ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events.</i></p> |
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Inotropes:

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| SURVIVE (2007) | <p>Aim: <i>To evaluate treatment with levosimendan compared with dobutamine among patients with acute heart failure in need of inotropic support.</i></p> <p>Study: <i>1327 patients hospitalized with acute decompensated heart failure who required inotropic support were randomized to levosimendan or dobutamine. Despite an initial reduction in plasma BNP level in patients in the levosimendan group, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes.</i></p> |
| DOREMI (2021) | <p>Aim: <i>To compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock.</i></p> <p>Study: <i>192 patients with cardiogenic shock were randomized to receive milrinone or dobutamine. There were no differences in the composite primary outcome or secondary outcomes between milrinone or dobutamine. The incidence of in-hospital death was high in both groups, without any differences in other adverse clinical outcomes between the two groups.</i></p> |

Vasodilators:

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| ROSE (2013) | <p>Aim: <i>To assess if low-dose dopamine or nesiritide will enhance decongestion and preserve renal function in setting of acute HF and renal dysfunction.</i></p> |
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| | <p>Study: 360 hospitalized patients with acute heart failure and renal dysfunction (eGFR of 15-60 mL/min/1.73 m²) were randomized within 24 hours of admission to dopamine (2 µg/kg/min) or nesiritide (0.005 µg/kg/min). Within each strategy, patients were randomized to active treatment or placebo. Neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.</p> |
| <p>ASCEND-HF (2011)</p> | <p>Aim: To evaluate the effect of nesiritide on symptoms at 6 and 24 hrs, HF rehospitalization or death from any cause at 30 days, and renal dysfunction.</p> <p>Study: 7141 patients with acute heart failure were randomly assigned to receive either nesiritide or placebo for 24 to 168 hrs in addition to standard care. Nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization and had a small, nonsignificant effect on dyspnea. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure.</p> |
| <p>RELAX-AHF-2 (2019)</p> | <p>Aim: to assess safety and efficacy of serelaxin, recombinant form of relaxin-2, which is a vasodilating hormone, in reducing CV mortality in acute HF.</p> <p>Study: 6545 patients who were hospitalized for acute heart failure and had dyspnea, vascular congestion on chest radiography, increased plasma concentrations of NPs, mild-to-moderate renal insufficiency, and a SBP ≥ 125 mmHg were randomly assigned within 16 hrs after presentation to receive either a 48-hr IV infusion of serelaxin (30 µg/kg/day) or placebo, in addition to standard care. The primary end points were CV death at 180 days and worsening HF at 5 days. Serelaxin infusion did not result in a lower incidence of CV death at 180 days or worsening heart failure at 5 days than placebo.</p> |
| <p>GDMT initiation and Uptitration:</p> | |
| <p>STRONG-HF (2022)</p> | <p>Aim: To evaluate the efficacy and safety of up-titration of standard oral heart failure medications during hospitalization for acute heart failure.</p> <p>Study: 1800 patients aged 18-85 years admitted to hospital with acute heart failure, not treated with full doses of GDMT, were randomly assigned before discharge to either usual care (followed usual local practice) or high-intensity</p> |

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| | care (up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and 4 scheduled outpatient visits over the 2 months after discharge). An intensive treatment strategy of rapid up-titration of GDMT and close follow-up after an AHF admission reduced symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care. |
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References and Suggested readings:

- Theresa A McDonagh, Marco Metra, Marianna Adamo, et al., ESC Scientific Document Group, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, *European Heart Journal*, Volume 42, Issue 36, 21 September 2021, Pages 3599–3726.
- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).
- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
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Chapter 3:

Mechanical Circulatory Support and Heart Transplant

Mechanical circulatory support (MCS) may be used as:

- **Bridge to decision (BTD)/Bridge to bridge (BTB):** Use of short-term MCS (ECMO or Impella) in patients with cardiogenic shock until haemodynamics and end-organ perfusion are stabilized, contraindications for long-term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated.
- **Bridge to candidacy (BTC):** Use of MCS (usually LVAD) to improve end-organ function and/or to make an ineligible patient eligible for heart transplantation.
- **Bridge to transplantation (BTT):** Use of MCS (LVAD, BiVAD or TAH) to keep a patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available.
- **Bridge to recovery (BTR):** Use of MCS (short-term or long-term) to keep a patient alive until cardiac function recovers sufficiently to remove MCS.
- **Destination therapy (DT):** Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation.

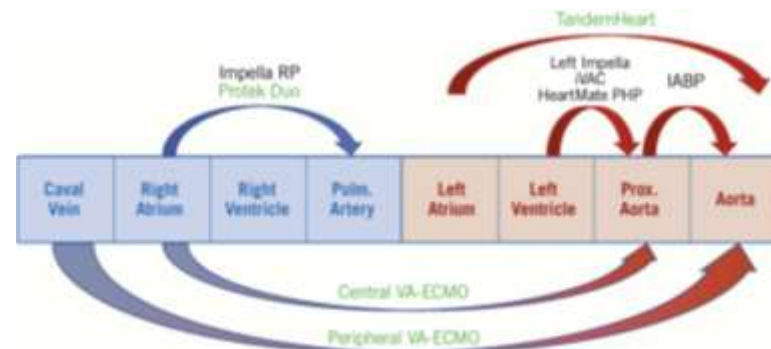


Figure 3-1: Different options for percutaneous mechanical circulatory support. Arrows indicate which part of the circulation is supported by the pVAD-modality. Devices in green can add blood oxygenation next to mechanical support. **Source:** Chieffo A, Dudek D, Hassager C, et al. Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. European Heart Journal Acute Cardiovascular Care. 2021 May 1;10(5):570-83.

Intra-aortic balloon pump (IABP)

Overview of IABP:

IABP is a balloon mounted on a catheter, inserted through a femoral artery (7-8 Fr sheath). It is placed just distal to the left subclavian artery (at the level of the *tracheal carina* fluoroscopically or between the 2nd and 3rd intercostal space as seen on chest X-ray) and extends proximal to the renal arteries. It has 2 lumens: **(i)** a helium gas ⁽¹⁾ line connected to the balloon, and **(ii)** a central arterial lumen attached to the monitor.

The IABP inflates in early diastole (i.e just at the diastolic notch) and deflates at end-diastole (i.e just at the isovolumic contraction phase before the aortic upslope), which results in:

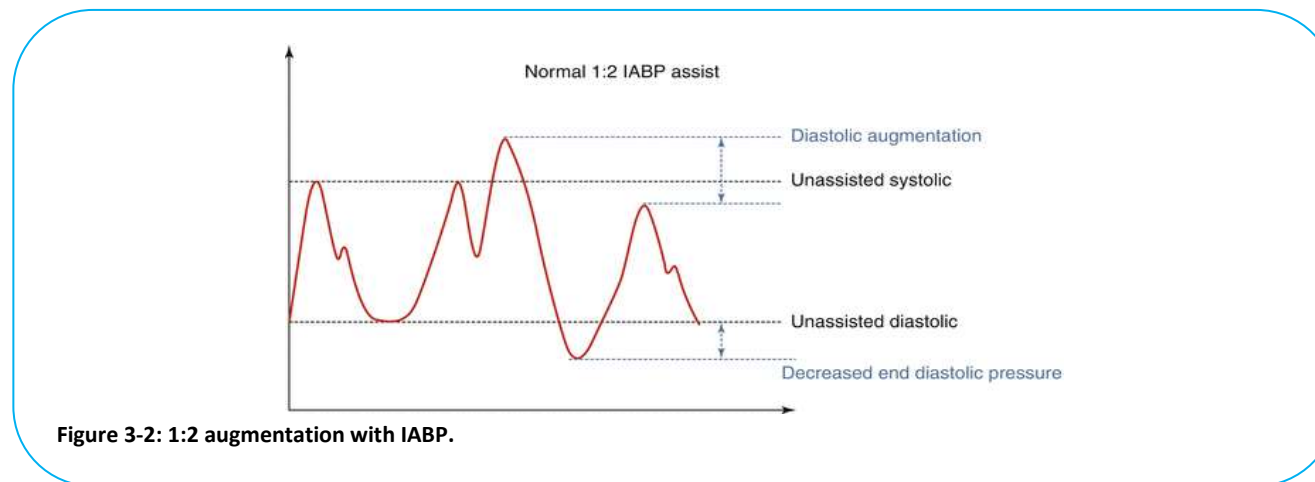
- IABP deflation in systole creates a negative pressure in the aorta that “sucks” flow from the LV, thus reducing afterload and myocardial wall stress. This increases cardiac output by ~20%, and decreases LV filling pressure and PCWP by ~20%. Furthermore, the reduction in afterload decreases myocardial O₂ demands, which reduces myocardial ischemia.

⁽¹⁾ Helium is used due to favourable flow characteristics (low density) and easy absorption into the bloodstream in case of balloon rupture.

- IABP inflation in diastole increases aortic diastolic pressure. In addition, IABP reduces LVEDP. Thus, IABP improves the gradient that drives coronary flow (aortic diastolic pressure minus LVEDP), which improves coronary flow in low-output states with non-obstructed coronary arteries.

Note that an IABP reduces systolic and end-diastolic BP, but creates a third component to BP, called **augmented BP**, that is higher than the unassisted systolic BP. The end-diastolic pressure should generally be reduced by ~10-15 mmHg in comparison to the baseline end diastolic pressure to ensure proper support. The mean arterial pressure increases, and more importantly cardiac output and tissue perfusion increase even if the mean arterial pressure is unchanged. Systemic pressure is not a parameter by which the efficacy of IABP should be gauged.

The IABP may be set to augment at a ratio of 1:1 (inflates every beat), 1:2 (inflates every other beat) or 1:3. The frequency may be reduced as a method of weaning from the IABP or to assess the heart's function without augmentation. It is also useful to see unassisted waveforms to diagnose timing errors with IABP.



Triggering and timing:

- The IABP is often timed and triggered to the **ECG**. It inflates at the end of T wave, which corresponds to the aortic valve closure and beginning of diastole, and deflates at the peak of R wave, which corresponds to the beginning of the isovolumic contraction. Adjustment of timing is rarely necessary with the current IABP systems, as these systems look at the aortic pressure and automatically fine-tune the timing.
- **The arterial waveform** can also be used for triggering and timing but should not be used in irregular rhythm, as the balloon may remain inflated between cardiac cycles. If the arterial lumen is thrombosed, a radial line may be used to monitor the arterial waveform but not to adjust the timing, as balloon inflation and deflation are seen relatively later on the radial waveform than on the aortic waveform.
- **Ventricular pacing spikes** may be used for timing of patients who are 100% ventricular-paced. In fact, even in patients who are paced, it is preferred to use the ECG for timing.
- **Internal mode** will set the balloon to inflate without a trigger in an asynchronous fashion at 80 bpm. This mode is rarely indicated. It is occasionally used with extra corporeal support.

Troubleshooting and lack of appropriate augmentation:

- **If there is no pressure augmentation and the helium balloon inflation waveform is flat or abbreviated**, consider gas leak (check tubing connections, check for blood in the gas lumen). Also, consider catheter kink and ensure that the balloon is fully out of the sheath.
- **A helium balloon inflation waveform that is overexpanding** suggests impaired balloon deflation (catheter is kinked or balloon is partially in the sheath).

Indications for IABP:

- Cardiogenic shock due to acute ischemia/infarction: IABP is used in conjunction with PCI, is placed before or after PCI, and kept until the patient stabilizes (IABP used as a bridge to recovery).
- Mechanical complications related to MI (ventricular septal rupture, papillary muscle rupture): IABP is used as a bridge to surgical treatment.
- In patients with low EF undergoing multivessel or left main PCI, planned IABP placement was associated with a significant reduction in 4-year mortality compared with no IABP or bailout IABP (BCIS-1 trial). IABP did not reduce the short-term mortality.
- Prophylactically, pre- and post-cardiac surgery in the following high-risk cases: severe LV dysfunction, ongoing ischemia, high-grade left main stenosis, decompensated AS.
- Refractory ischemic arrhythmias: IABP is placed during revascularization, or after revascularization if these arrhythmias persist.

IABP is a temporizing measure, a bridge to a more definitive therapy (CABG, PCI). It is also a supportive measure pending an expected recovery after a complicated PCI or CABG with transient stunning.

Contraindications:

- Moderate or severe AI.
- Abdominal aortic aneurysm.
- Aortic stents or grafts.
- HOCM (since intracavitary obstruction increases with afterload reduction).
- Severe peripheral arterial disease is a relative contraindication. Rather than being due to the balloon itself, *limb ischemia is related to the sheath* occluding flow to the ipsilateral limb. The use of a sheathless IABP limits limb ischemia, but sheathless insertion is contraindicated in severely obese patients because of the risk of subcutaneous catheter kink.

Complications

- Insertion complications (pseudo aneurysm formation, bleeding, vascular injury).
- Aortic damage.
- Systemic embolization.
- Limb ischaemia.
- Compartment syndrome.
- Haematological effects (haemolysis and thrombocytopenia).
- Malpositioning causing arterial occlusion:
 - Too high → myocardial ischaemia in patients with left internal mammary artery (LIMA) to left anterior descending (LAD) coronary artery if the left subclavian artery is occluded.
 - Too low → renal and mesenteric ischaemia.
- Timing errors worsening myocardial oxygen supply- demand ratio.
- Balloon rupture (if blood enters balloon lumen may clot and cause difficulty in removing).
- Infection

Care and follow-up:

- Daily chest X-rays are performed to check the catheter position.
- IV therapeutic doses of heparin (goal PTT 46-70s) are provided to: **(i)** prevent limb ischemia from the large sheath, **(ii)** prevent thrombosis over the balloon.
- Daily CBC, as IABP may lead to hemolytic anemia and mild thrombocytopenia. *Severe thrombocytopenia is not secondary to IABP.*

Weaning:

- The IABP is weaned off when the patient is stable, usually 24-48 hrs after placement, and after appropriate therapy of the underlying cardiac condition. The patient must be:
 - Hemodynamically stable with or without small doses of inotropes/vasopressors, and preferably with the support of vasodilators that will simulate the IABP effect if the blood pressure allows.
 - Stable from the ischemic standpoint.
- When the patient is ready to be weaned off, there are two ways for weaning:
 - **Augmentation Weaning:** Currently it is the preferred method as it is more physiological. The IABP augmentation may be weaned in 10% increments, if tolerated, every 30 minutes. The augmentation should not be reduced below 50% as this increases the risk of thromboembolic complications.
 - **Frequency weaning:** Reducing the frequency from 1:1 to 1:2 and then potentially 1:3. This is not recommended as with the change of 1:1 to 1:2 frequency, diastolic coronary blood flow is reduced by more than 50% and so is considered much less controlled than augmentation weaning.
- During the weaning process, assess for:
 - Chest pain or ischaemic ECG changes
 - Pulmonary oedema
 - Confusion, tachycardia or hypotension
 - Reduced cardiac output and elevated filling pressures.
- If the patient tolerates weaning, IABP may be removed. Heparin is held for ~2 hrs and 1:1 pumping is resumed during these hours to prevent balloon clotting. The pump is shut off and IABP removed when ACT < 160 s or PTT < 50 s.
- The IABP should never be left switched off due to the risk of clot formation and systemic embolization.

Causes of lack of appropriate pressure augmentation:

1. **Late inflation or early deflation** (leads to suboptimal increase in coronary perfusion and suboptimal sucking effect).
2. **Late balloon deflation or early inflation** (balloon inflated in systole increases afterload).
3. **Shock state that is not cardiogenic** in nature, such as hypovolemic shock or septic shock. In septic shock, afterload is already reduced and IABP does not further increase stroke volume.
4. **Tachycardia > 120 bpm** reduces diastolic time, and thus reduces balloon filling and inflation during this brief time. The reduced diastolic time during each cardiac cycle is the main issue, rather than a limited ability to circulate gas at high rates; switching to 1:2 does not necessarily help.
5. **Balloon kinking** may lead to poor augmentation or poor deflation. Check the catheter and tubing for a visible kink, ensure the balloon has fully exited the sheath and get an X-ray, and position the patient flat, as bending the groin area may kink the catheter.
6. **Gas leak due to loose connections or balloon leak/rupture.** The latter may result from inflation against calcified aortic plaques and may lead to clotting inside the balloon and balloon entrapment. The balloon inflation waveform is abbreviated and **blood is seen coming out of the gas lumen**. IABP should be placed on standby and **removed quickly** (< 30 min), to prevent balloon clotting and entrapment.

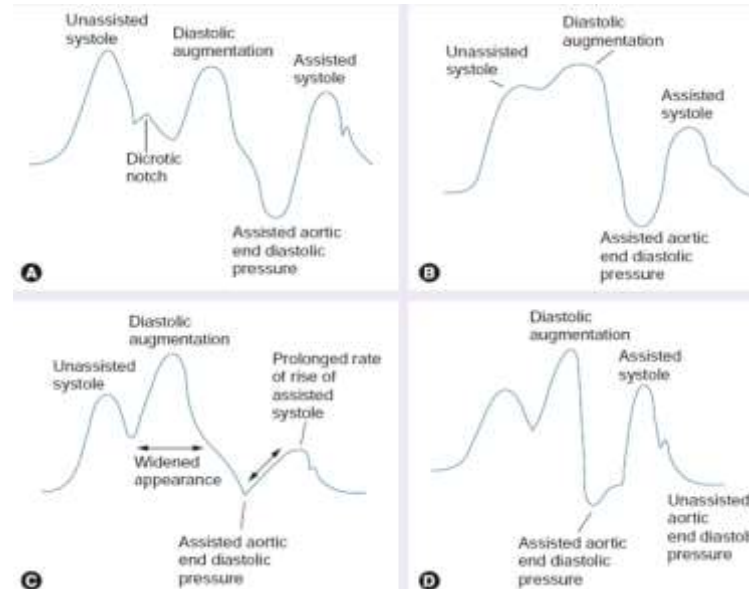


Figure 3-3: Systemic arterial pressure waveforms of common errors encountered during IABP. (A) Late inflation, (B) Early inflation, (C) Late deflation and (D) early deflation. Source: Trost JC, Hillis LD. Intra-aortic balloon counterpulsation. The American journal of cardiology. 2006 May 1;97(9):1391-8.

Impella or transvalvular LV assist device

Impella is the prototype transvalvular LV assist device. It is a small axial flow pump placed across the aortic valve, aspirating blood from the LV into the ascending aorta. The flow is continuous not pulsatile.

Impella is manufactured in three versions: **2.5 device** (12 Fr, maximum flow 2.5 L/min), **CP device** (14 Fr, maximum flow 2-4 L/min), and **5.0 device** (21 Fr, maximum flow 5 L/min). Impella 5.0 is not fully percutaneous and requires a surgical procedure to insert a 21 Fr catheter in the femoral artery. The Impella device is FDA approved for partial support of up to 6 days, and it has a CE mark for up to 5 days.

In addition to increasing cardiac output, Impella reduces the end-diastolic volume (preload) and the end-systolic volume (wall tension or afterload), which reduces O₂ demands. The reduction in end-diastolic pressure also improves subendocardial perfusion and microcirculatory flow.

The more Impella contributes to the cardiac output, the less pulsatile the blood flow is. For example, during coronary balloon inflation in high-risk coronary intervention, the pulse pressure is severely reduced and the aortic pressure may become a flat pressure line provided by Impella.

It is important to maintain adequate preload during Impella therapy, as a low preload reduces the benefit from Impella and its potential to increase the overall cardiac output. It is also important to maintain a low arterial afterload (mean BP < 90 mmHg), as the axial pumping is impeded by a high aortic pressure.

Complications:

Major complications include: vascular injury, bleeding, thrombosis, haemolysis, and device migration.

Contraindications:

- Moderate or severe AS or AI, as the Impella catheter may worsen the aortic pathology.
- Implanted mechanical aortic valve.
- Presence of LV thrombus.
- Inability to anticoagulate patients.
- Severe peripheral arterial disease is a relative contraindication.

Hemodynamic differences between IABP and Impella:

- Impella reduces afterload differently from IABP: the former reduces LV volume (flow device) while the latter reduces aortic resistance (pressure device). However, the two devices should not be combined. The diastolic augmentation of IABP increases the diastolic afterload of Impella, which is a continuous pump, and counteracts the Impella flow in diastole. This drastically

reduces the diastolic and overall Impella flow. Besides, significant hemolysis may occur as the Impella pumps against an inflated balloon.

- Impella provides a constant axial flow, and, as opposed to IABP, there is no need for ECG or pressure waveform synchronization.
- With IABP, the absolute increase in cardiac output depends on the baseline cardiac output; thus, in the sickest patients with severe heart failure and limited cardiac reserve, cardiac output may only increase by 0.2 L/min, which necessitates the adjunctive use of inotropic agents. The benefit of IABP in this context is mainly seen in terms of reducing myocardial ischemia. Impella 2.5, on the other hand, increases cardiac output by 2.5 L/min in the most severe cases of HF. Thus, Impella further improves cardiac output in severe LV failure while unloading the LV and reducing O₂ demands. The patient is less likely to require inotropic agents with Impella than with IABP support.
- Due to its superior flow, Impella CP is used in cardiogenic shock, while Impella 2.5 is used to support PCI.
- In an animal study of cardiogenic shock, *Impella improved coronary flow in unobstructed coronary arteries by up to ~45%, significantly more than IABP (~15%).* Impella improves coronary flow through the increase in mean arterial pressure but also through the reduction of LVEDP and microvascular resistance. Moreover, *Impella unloads the LV and reduces O₂ demands more dramatically than IABP.*

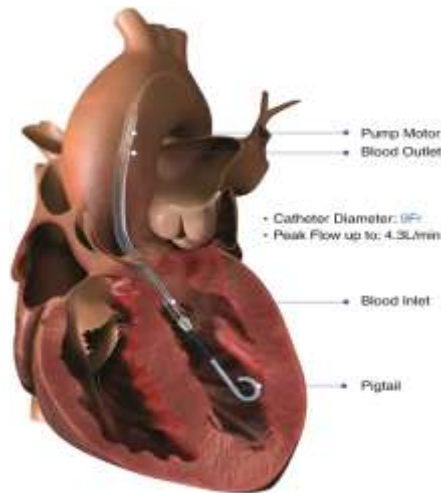


Figure 3-4: Impella components.

TandemHeart LV assist device

- TandemHeart connects the left atrium with the iliofemoral artery. TandemHeart consists of: **(i)** Inflow cannula (21 Fr; inserted via the femoral vein to the right atrium and trans-septally into the left atrium), **(ii)** Centrifugal continuous extracorporeal blood pump, and **(iii)** Outflow arterial cannula (15 or 17 Fr).
- A membrane oxygenator can be added to the TandemHeart circuit to provide respiratory support.
- The maximum output depends on the diameter of the outflow cannula (3.5 L/min in case of 15 Fr outflow cannula and 5 L/min in case of 17 Fr outflow cannula).
- In order to prevent limb ischemia from the large arterial cannula, a sheath is placed antegradely in the femoral artery and connected in a Y fashion with the iliac cannula.
- The main advantages of this device are the direct unloading of the left atrium which results in a decrease in LV filling pressures, volumes and oxygen demand and that it does not require passage into the LV. However, positioning of the cannula in the left

atrium carries a risk of complications, such as perforation, or most frequently, cannula migration to a suboptimal position or back to the right atrium. Other complications include vascular site complications, infections, and thromboembolic incidents.

- The major disadvantage is the immobility of the supported patient; care providers must secure the inflow cannula since movement of the tip from the left to right atrium results in significant right-to-left shunting with catastrophic desaturation.
- While Impella and TandemHeart provide good hemodynamic support and myocardial ischemic protection, Impella 2.5 is likely more suited for high-risk PCI or MI, where ischemic protection is the primary concern, whereas TandemHeart is likely more suited for cardiogenic shock, where hemodynamic support is the primary concern. The availability of Impella CP, which provides both ischemic protection and large flow rate, has lessened the need for TandemHeart.

Extracorporeal membrane oxygenation (ECMO)

ECMO is a cardiopulmonary bypass machine modified for easier and longer use and transport. ECMO can be used in either veno-arterial or veno-venous configurations. The veno-arterial (VA) mode provides full cardiopulmonary support, while the veno-venous (VV) mode provides only respiratory support, and it is used in cases of severe respiratory failure with preserved cardiac output.

Venoarterial (VA) ECMO:

All VA-ECMO circuits consist of: **(i)** a venous (inflow, drainage) cannula, **(ii)** a pump, **(iii)** an oxygenator, and **(iv)** an arterial (outflow, return) cannula. ECMO provides flow at ~4:6 L/min.

VA ECMO provides cardiopulmonary support by draining venous blood from the right atrium and returning it after oxygenation to the ascending aorta (Central ECMO) **or** to the iliac artery (Peripheral ECMO).

Patient Selection:

ECMO is particularly useful in:

1. Patients with **witnessed cardiac arrest** who had an immediate start of cardiopulmonary resuscitation, yet a lack of return of spontaneous circulation in > 10 min. *ECMO may be placed at the bedside in a patient with cardiac arrest and ongoing chest compressions, using groin access.*
2. Patients with **profound cardiogenic shock and biventricular failure**, where LV support alone with Impella may not be enough. This may apply to patients with fulminant myocarditis with severe haemodynamic impairment or massive pulmonary embolism and arrhythmic storm.

The overall survival rate using peripheral VA-ECMO in cardiac arrest and refractory cardiogenic shock remains generally reported between 29% and 41% respectively. No randomized controlled studies have been undertaken, largely because of the logistical, legal, and ethical issues.

Absolute contraindications:

- Extracorporeal CPR with unknown downtime, unwitnessed, unknown neurological status.

- Terminal illness with < 2 years expected survival.
- Multi-organ system failure.
- More than trivial AI.
- Severe coagulopathy.
- CNS bleeding.
- Irreversible CNS dysfunction.

Cannulation strategies:

ECMO can be configured with central or peripheral access:

- **Central ECMO** requires surgical access and cannulation of the ascending aorta, and it is predominantly used for postcardiotomy short-term MCS in patients who fail to wean off cardiopulmonary bypass.
- Conversely, **peripheral ECMO** can be placed by interventional cardiologists or trained intensivists using the Seldinger technique for insertion of cannulas in the femoral artery and vein for patients with refractory cardiogenic shock and cardiac arrest. ECMO drains unoxygenated blood from the IVC and returns oxygenated blood through the femoral artery. In the absence of any forward cardiac output, blood will retrogradely flow from the femoral artery towards the upper body.

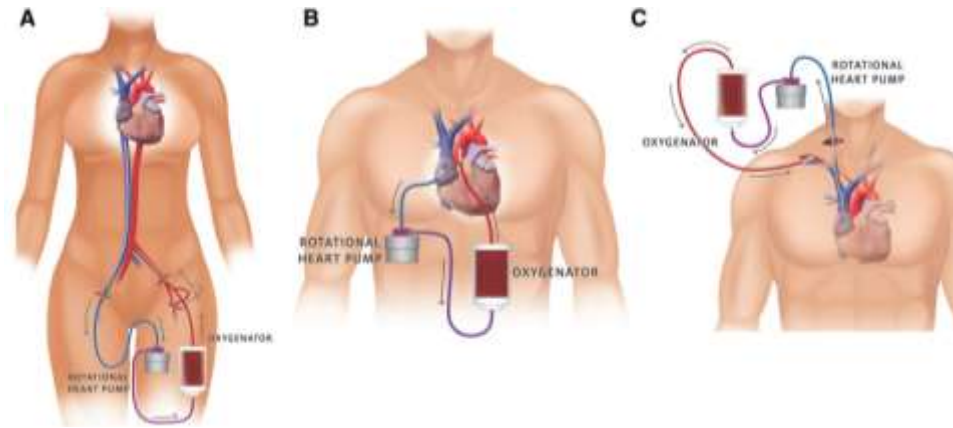


Figure 3-5: Central and peripheral VA-ECMO cannulation strategies. A) Peripheral VA-ECMO (femoro-femoral configuration). B) Central VA-ECMO. C) Peripheral VA-ECMO (sport configuration). **Source:** Rao P, Khalpey Z, Smith R, et al. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: cardinal considerations for initiation and management. *Circulation: Heart Failure*. 2018 Sep;11(9):e004905.

Main hemodynamic considerations during VA-ECMO:

- **LV Distension:**

- Although ECMO provides full support for the patient, it may have non-physiologic and sometimes detrimental haemodynamic consequences on the myocardium. Draining blood from the venous side results in a reduction of preload to the heart, and, consequently, reduces filling pressures of both ventricles. On the arterial side, ECMO delivers 4-6 L/min of flow to the aorta resulting in increased the LV afterload and may make it harder for the intrinsic LV to open the aortic valve. Therefore, ECMO in itself does not necessarily decompress the heart, and depending on the severity of myocardial dysfunction and presence of AR or MR, peripheral VA ECMO may even increase LV end-diastolic pressures and volumes. The resulting pulmonary venous congestion may lead to pulmonary oedema and compromise respiratory function. In these cases, a few modifications in the

ECMO circuit can be performed to optimize support, such as inserting a left atrial vent for unloading the pulmonary veins/left atrium, or adding a second device to unload the LV [e.g. IABP, or Impella] ⁽¹⁾.

- There are several clinical indexes used to monitor and identify patients at risk of LV distention:
 - Presence and degree of aortic valve opening can be detected on the arterial pulse pressure tracing.
 - Echocardiography can be used to directly visualize the extent and duration of aortic valve opening (M-Mode through the aortic valve is helpful to determine whether the aortic valve opens, and if so the degree and frequency of valve opening) ⁽²⁾.
 - Progressive hypoxia in blood exiting the LV detected by checking the arterial O₂ saturation of the right radial artery (furthest away from ECMO flow). It can signify perfusion of the superior circulation with deoxygenated blood because of worsening pulmonary edema.
 - Worsening pulmonary edema on a chest x-ray can signify worsening PCWP. However, this can be a late finding and is nonspecific.
 - Pulmonary artery catheter (PAC) is the best index of LV filling pressures.
- **Inflammatory reaction:** VA-ECMO is associated with inflammatory reaction akin to that in systemic inflammatory response syndrome. This inflammatory response arises as a result of blood exposure to the non endothelialized surface of the ECMO circuit leading to activation of the innate immune system.
- **North-south (Harlequin) syndrome and the watershed region:**
 - Because of the retrograde flow support in the setting of peripheral VA-ECMO, blood travels in the direction opposite to normal; retrograde from the femoral or iliac artery back toward the thoracic aorta. Therefore, in patients receiving peripheral VA-ECMO, there is an area of watershed, which is the region within the aorta where the 2 blood streams meet. This watershed region can lie anywhere between the aortic root and diaphragm depending on the output of the LV relative to ECMO flow.
 - Although blood derived from the ECMO circuit is typically well oxygenated, blood exiting the LV is dependent on adequate pulmonary gas exchange, which is often impaired in the setting of cardiogenic shock and pulmonary edema. Therefore, if the

(1) In a patient with cardiac arrest, ongoing chest compressions should be continued to vent the LV.

(2) LV chamber size measured during ECMO support can be misleading as an index of ventricular distention, LVEDP, and PCWP.

watershed region is located distal to the left subclavian artery, there may be considerable risk of hypoxemia to the brain, heart, and upper extremities. In extreme circumstances, this may lead to *Harlequin syndrome*, also known as *north-south syndrome*. This is when venous blood (i.e, blue blood) passing through lungs with impaired oxygen diffusion capacity (e.g, because of pulmonary edema) is ejected by the LV into the ascending aorta to perfuse the upper body and brain. Meanwhile, venous blood drained by the venous cannula passes through the ECMO circuit and perfuses the lower body with well-oxygenated blood (i.e, red blood). This leads to differential cyanosis with upper body hypoxemia and lower body hyperoxia. Treating pulmonary pathology and increasing ventilator support (to improve blood oxygenation) may help in overcoming this phenomenon.

- Assessment of the pulse pressure at the right radial artery is helpful in locating the watershed region. ECMO flow is nonpulsatile, and as such, a narrow pulse pressure at the right radial artery indicates a watershed in the aortic root. By contrast, a wide pulse pressure at the right radial artery suggests a watershed region distal to the innominate artery.

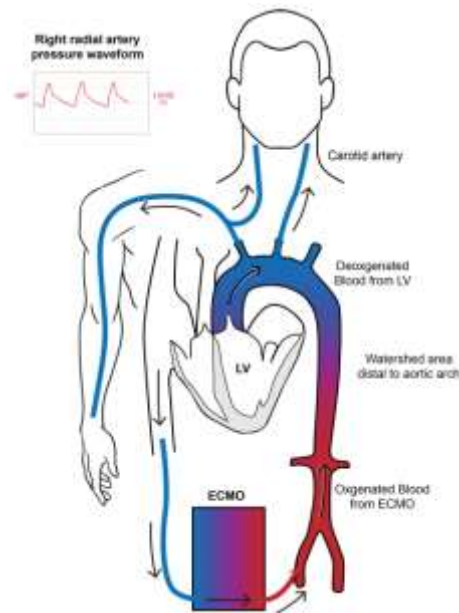


Figure 3-6: North-south (Harlequin) syndrome: a common consideration with femoral artery cannulation and when the lungs are not adequately oxygenating blood. **Source:** Rao P, Khalpey Z, Smith R, et al. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: cardinal considerations for initiation and management. *Circulation: Heart Failure*. 2018 Sep;11(9):e004905.

Anticoagulation Strategy for Peripheral VA-ECMO:

VA-ECMO and its attendant prothrombotic inflammatory environment increase the risk of thrombosis, which may cause pump malfunction, oxygenator failure, and thromboembolic events. However, major bleeding is reported to occur in roughly one quarter of all VA-ECMO patients and can happen in patients without anticoagulation therapy. It is recommended to use unfractionated heparin targeting an activated clotting time (ACT) of 180 to 220 seconds.

Weaning:

The SAVE score (www.save-score.com) can be used as a tool to predict survival in patients with cardiogenic shock in which ECMO is considered. After a few days, ECMO is weaned off by progressively reducing its flow to 1.5 L/min while monitoring systemic pressure and LV function by echo. Before removal, the cannulae are clamped for 15 minutes to ensure hemodynamic stability. Vasopressors may need to be up-titrated during the weaning process. Pulmonary edema may worsen as venous return increases. As an alternative to ECMO in patients with biventricular failure and shock requiring temporary support, an **extracorporeal biventricular assist device** may be used (CentriMag BiVAD). The cannulae of the right assist device are surgically placed in the RA and PA, while the cannulae of the left assist device are surgically placed in the LV (or LA) and the aorta. The pump, and the optional oxygenator, are outside the body. BiVAD is more effective than ECMO and may be used for 30 days (as opposed to a few days only for ECMO).

Veno-venous ECMO

Drains blood from a femoral venous access and returns it into a jugular venous access. It is used in patients with preserved circulation but severe respiratory failure e.g., acute respiratory distress syndrome (ARDS).

Table 3-1: Characteristics of short-term mechanical circulatory support.

| | IABP | Impella | TandemHeart | VA-ECMO |
|------------------|---|-----------------------------------|--|--|
| Insertion | <i>Femoral or axillary artery to AO</i> | <i>LV to AO</i> | <i>- Venous cannula: femoral vein to LA - Arterial cannula: iliac artery</i> | <i>- Venous cannula: RA - Arterial cannula: iliac artery</i> |
| Mechanism | <i>Diastolic augmentation of aortic pressure and improved LV performance via systolic</i> | <i>Expels blood from LV to AO</i> | <i>Aspirates oxygenated blood from LA and returns to iliac artery</i> | <i>Drainage of deoxygenated venous blood, via an extracorporeal centrifugal pump over a membrane</i> |

| | | | | |
|-------------------------------------|---|--|--|---|
| | <i>balloon deflation (decrease in afterload)</i> | | | <i>oxygenator and pumped back oxygenated blood to iliac artery</i> |
| LV unloading | (+) | (++) | (++) | <i>LV overloading in peripheral ECMO</i> |
| Technical characteristics | <i>Cannula size: 7-8 F Cardiac output: 0.3-0.5 L/min Pulsatile flow</i> | <i>- Cannula size: 12-14 F for (CP) and 21 F for (Impella 5.0) - Cardiac output: 2.5-5.0 L/min - Continuous flow via axial pump with max speed of 51000 r.p.m.</i> | <i>- Cannula size: 21 F (venous) and 12-19 F (arterial) - Cardiac output: 4 L/min - Continuous flow via centrifugal pump; maximum pump speed 7500 r.p.m.</i> | <i>- Cannula size: 19-25 F (venous) and 15-19 F (arterial) - Cardiac output: up to 7 L/min - Continuous flow via centrifugal pump with a maximum speed of 5000 r.p.m.</i> |
| Duration | <i>Days to weeks</i> | <i>10 days for Impella 2.5 and CP 3 weeks for Impella 5.0</i> | <i>2-3 weeks</i> | <i>3-4 weeks and occasionally longer</i> |
| Advantages | <i>Easy insertion, easy to adjust, cath lab not mandatory, no extracorporeal blood; increase coronary and cerebral flow</i> | <i>ECG and pulse independent relatively easy insertion in cath lab, no extracorporeal blood</i> | <i>- Rhythm independent, less artificial surface than ECMO - Can be used in cases of AS/prosthetic aortic valve; and even in LV thrombus</i> | <i>Rhythm independent, rapid insertion, full circulatory support even in resuscitation situations or during malignant arrhythmia, rapid improvement in oxygenation</i> |
| Disadvantages/ complications | <i>- ECG/pulse dependent (mostly inefficient in</i> | <i>Limb ischaemia Haemolysis</i> | <i>Limb ischaemia Bleeding Complex implantation</i> | <i>- Haemolysis, thromboembolic complications renal failure,</i> |

| | | | | |
|--------------------------|--|---|---|--|
| | <i>tachycardia & irregular rhythm)</i> - <i>Limb ischaemia</i> - <i>Haemolysis, Thrombocytopenia</i> - <i>Infection</i> | <i>Bleeding</i> <i>Infection</i> | <i>requiring transseptal puncture</i> <i>Infection</i> | <i>limb ischemia/amputation, infection and bleeding</i> - <i>LV overloading: peripheral cannulation is associated with an increase in LV afterload.</i> - <i>Harlequin syndrome.</i> |
| Contraindications | - <i>Moderate to severe aortic regurgitation</i> - <i>Severe aortic disease</i> | - <i>Severe AS, Prosthetic aortic valve</i> - <i>LV thrombus</i> - <i>VSD</i> - <i>Peripheral vascular disease</i> | - <i>Severe aortic insufficiency</i> - <i>Aortic dissection</i> - <i>Peripheral vascular disease</i> - <i>RV failure</i> - <i>VSD</i> - <i>Inability to tolerate anticoagulation</i> | - <i>Severe aortic insufficiency</i> - <i>Aortic dissection</i> - <i>Inability to tolerate anticoagulation</i> |

Left ventricular assist device (LVAD)

LVAD supports the LV and consists of: **(i)** a pump, **(ii)** an inflow cannula inserted in the apex and **(iii)** an outflow cannula inserted in the ascending aorta. Those three components are intracorporeal, with the pump in the preperitoneal or pericardial space; in older devices, the pump was extracorporeal. The pump is connected to an external battery through a transcutaneous driveline, a potential source of infection.

Right ventricular assist device (RVAD) supports the RV, the inflow cannula being inserted in the RA or RV and the outflow cannula in the PA. BiVAD consists of LVAD and RVAD. RVAD is not as effective in supporting the right circulation as LVAD is for the left circulation. This is because the RVAD pump often leads to a severe increase in PA pressure, particularly over long-term use.

Among patients with continuous flow LVADs, survival rate was 80% at 1 year and 70% at 2 years.

Types of ventricular assist devices:

There are several pump designs:

1. The first-generation devices, such as HeartMate, have a **pulsatile pump with two valves**. Despite improving mortality, the HeartMate device had a high malfunction rate of 35% at 2 years in the REMATCH trial, which translated into a drop of 2-year survival to 24% (yet much better than no device).
2. **Continuous-flow axial pump**, such as HeartMate II: since no reservoir is needed, these devices are much smaller and require less energy, with less risk of malfunction. In comparison with HeartMate device, the HeartMate II device was associated with a substantially lower rate of reoperation to repair or replace the pump at 2 years (10% vs. 36%), and less infection and bleeding (less surgical dissection), which translated into a better 2-year survival (58% vs. 24%).
3. **Continuous-flow centrifugal pump**, such as HeartMate III and HeartWare: The fully magnetically levitated centrifugal-flow LVAD has significantly reduced pump thrombosis. In MOMENTUM 3, the need for reoperation to replace a malfunctioning device was 2.3% per 2 years (Only 0.6% due to thrombosis).

Continuous-flow LVADs have a number of major advantages over previous pulsatile technology:

- Continuous-flow pumps eliminate the need for a blood pumping chamber and volume compensation.
- A lighter, smaller pump is better suited for patients with a smaller body size.
- Simple designs include only 1 internal moving part, the rotor, and no internal valves.
- They are silent in operation.
- The benefits of the smaller percutaneous lead: reduced infection risk and greater patient comfort.
- The flow generated by the continuous-flow devices depends on the pump's "*delta pressure*" (Delta pressure= Outflow pressure (aorta) - Inflow pressure). The lower this delta pressure, the higher the flow. A higher outflow pressure translates into a lower pump flow, hence the importance of keeping a low afterload (mean BP < 90 mmHg) and a high preload.

The following LVAD parameters are displayed:

1. **Pump speed**, in rpm, is the only adjustable LVAD variable.

- 2. Power** is the energy generated by the LVAD. Power inversely correlates with the resistance that opposes the LVAD pump (delta pressure).
- 3. Pulse index** corresponds to how much cardiac output is generated by the native LV. The lower the pulse index, the higher the amount of support provided by the pump.
- 4. Flow** correlates with power and is estimated based on pump power and speed, and blood viscosity (hemoglobin). Pump speed is the only adjustable LVAD variable; power and pulse index are measured by LVAD; flow is not directly measured but calculated.

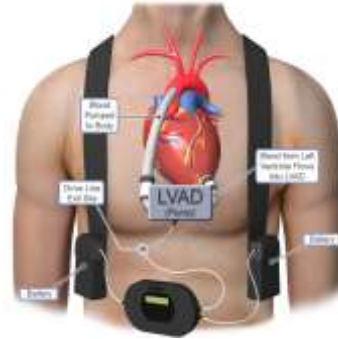


Figure 3-7: LVAD components.



Figure 3-8: LVAD types on chest x-ray.

Indications for LVAD:

Patients with persistence of severe symptoms despite optimal medical and device therapy, without severe RV dysfunction and/or severe TR, with stable psychological background and absence of major contraindications, and who have at least one of the following:

1. LVEF < 25% **and** unable to exercise for HF or with peak $\text{VO}_2 < 12 \text{ mL/kg/min}$ and/or < 50% predicted value (if able to perform cardiopulmonary exercise testing).
2. ≥ 3 HF hospitalizations in previous 12 months without an obvious precipitating cause.
3. Dependence on i.v. inotropic therapy or temporary MCS.
4. Progressive end-organ dysfunction (worsening renal and/or hepatic function, type II pulmonary hypertension, cardiac cachexia) due to reduced perfusion and not to inadequately low ventricular filling pressure ($\text{PCWP} \geq 20 \text{ mmHg}$ and $\text{SBP} \leq 90 \text{ mmHg}$ or cardiac index $\leq 2 \text{ L/min/m}^2$).

LVADs may be used as a:

- **Bridge to transplant:** They help stabilize patients so they can tolerate medical therapy. They improve organ perfusion, PA pressure and make patients better candidates for transplant.
- **Destination therapy:** In the REMATCH trial, HeartMate LVAD drastically improved survival in patients who were not transplant candidates (survival at 1 year was 52% with LVAD vs. 25% without LVAD).
- **Bridge to myocardial recovery:** Many patients with non-ischemic cardiomyopathy improve significantly with the LVAD and medical therapy, and LVAD may be explanted after 1-2 years (~15-20%).

Contraindications for LVADs:

○ **Absolute:**

- Coumarin intolerance.

- Absence of trained caregivers (i.e living alone is LVAD contraindication).
- Severe psychiatric disorders or non-adherence to the staff instructions.
- Severe motor deficit or cognitive deficit related after stroke.
- Neoplastic disease with unfavorable prognosis.
- Vascular malformation of the small bowel that predisposes to bleeding.
- Severe pulmonary obstructive disease.
- Severe hepatic dysfunction.
- Ventricular arrhythmias.
- Active infection.
- Hematologic changes (platelets < 50,000/mm³ and thrombophilia).

○ **Relative:**

- Difficult-to-control diabetes
- Partial motor deficit after stroke
- Severe malnutrition
- Significant peripheral artery disease
-

Management of Concomitant Cardiac Conditions:

Table 3-2: 2019 EACTS Expert Consensus recommendations for management of concomitant Cardiac conditions in patients with LVAD implantation:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| Aortic valve and root diseases: | | |
| <i>Replacement of a mechanical aortic valve with a biological valve is recommended.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Biological valve replacement in patients with more than mild aortic insufficiency should be considered ⁽¹⁾.</i> | IIa | C |
| <i>Surgical correction of an ascending aorta aneurysm at the time of implantation of a ventricular assist device should be considered.</i> | IIa | C |
| Mitral valve disease ⁽²⁾: | | |
| <i>Correction of moderate or severe mitral stenosis of any cause is recommended.</i> | I | C |
| <i>In selected patients, the repair of severe mitral insufficiency may be considered.</i> | IIb | C |
| <i>Exchange of a functional mitral mechanical or biological prosthesis at the time of long-term mechanical circulatory support device implantation is not recommended.</i> | III | C |
| <i>In patients previously treated with a MitraClip, a thorough evaluation to rule out the existence of mitral valve stenosis is recommended.</i> | I | C |
| Tricuspid valve disease and RV dysfunction ⁽³⁾: | | |
| <i>Correction of severe tricuspid stenosis is recommended.</i> | I | C |
| <i>Implantation of a biventricular assist device or a total artificial heart in patients with severe tricuspid regurgitation and RV dysfunction may be considered.</i> | IIb | C |
| Intracardiac shunts: | | |

-
- (1)** Patients with severe AI need to have AVR concomitant to LVAD placement, to avoid a closed loop circulation between the LV and the aorta. Bioprosthetic rather than mechanical AVR is used to reduce the risk of thrombosis of this unloaded valve. **N.B:** AR after LVAD should be upgraded by one grade based on traditional criteria. This is because the AR is both systolic and diastolic.
- (2)** Mitral regurgitation generally does not require repair. Mitral stenosis will limit pump flow while maintaining a high left atrial pressure which cause persistent pulmonary hypertension and RV dysfunction. So, Mitral stenosis to a moderate degree or greater must be corrected with mitral valve replacement with a bioprosthetic valve.
- (3)** Moderate to severe tricuspid insufficiency should be considered for repair to optimize RV function. This is especially important for patients with pulmonary HTN. Tricuspid valve repair can be performed using annuloplasty repair.

| | | |
|--|------------|----------|
| <i>PFO closure, either percutaneously or at the time of LT-MCS implantation, is recommended.</i> | I | C |
| <i>VSD closure during LT-MCS implantation is recommended.</i> | I | C |
| <i>In patients with an unreparable VSD, LT-MCS implantation is not recommended.</i> | III | C |
| Arrhythmia: | | |
| <i>Routine implantation of an implantable ICD for primary prophylaxis before long-term mechanical circulatory support implantation is not recommended.</i> | III | C |
| <i>In patients with refractory, recurrent VT/VF in the presence of an untreatable arrhythmogenic substrate (e.g. giant cell myocarditis or sarcoidosis), implantation of a biventricular assist device or a total artificial heart should be considered.</i> | IIa | C |
| Intracardiac thrombus: | | |
| <i>In patients with AF, due to the increased risk of thromboembolism from the LAA, a transoesophageal echocardiogram should be considered.</i> | IIa | C |
| <i>If LA or LV thrombus is present, inspection and removal of the thrombus are recommended.</i> | I | C |
| <i>If an LAA thrombus is present, occlusion of the LAA should be considered.</i> | IIa | C |
| <i>Although RV and RA thrombi are less common, cardiac imaging to exclude them, in particular before implantation of an RVAD, should be considered.</i> | IIa | C |
| Miscellaneous conditions: | | |
| <i>Left thoracotomy approach may be considered in patients who have prior cardiac surgery.</i> | IIb | C |
| <i>LT-MCS implantation in patients who have active infective endocarditis is not recommended.</i> | III | C |

Relation between LVAD and RV function:

- Fixed pulmonary hypertension, a contraindication to heart transplantation, but it is not a contraindication for LVAD, which frequently allows the reversal of pulmonary hypertension. In fact, in patients with RV dysfunction, *a high PA pressure may be more favorable for LVAD implantation than a normal PA pressure, as a high PA pressure predicts better RV function.*

| Table 3-3: Desired values indicating the least risk of RV failure after LVAD implantation: | |
|--|------------------------------|
| Parameter | Desirable value |
| Right ventricular stroke work index (RVSWI) ⁽¹⁾ | 5-10 g/m/beat/m ² |
| Central venous pressure | < 15 mmHg |
| Tricuspid regurgitation | Minimal to moderate |
| Pulmonary vascular resistance | < 4 W.U |
| Transpulmonary gradient | < 15 mmHg |
| RV size: | |
| - RVEDV | < 200 ml |
| - RVESV | < 177 ml |
| Need for pre-op ventilator support. | None |

(1) RVSWI was calculated by the formula: $0.0136 \times \text{stroke volume index} \times (\text{mean pulmonary artery pressure} - \text{right atrial pressure})$.

- RV failure is a major complication that occurs in up to 20% of patients post-LVAD and is predicted by the presence of elevated RA pressure (RA pressure > 20 mmHg or RA pressure > $0.65 \times \text{PCWP}$), reduced RVSWI, or signs of RV dysfunction on echocardiography (e.g RV GLS < 9.6%; 3D RV EF < 20%).
- RV failure requiring RVAD support is the most important risk factor for early death in LVAD recipients due to the inability of the RV to pump sufficient blood through the pulmonary circuit to fill the left heart.
- LV unloading by LVAD is beneficial for the RV, and the RV eventually improves in most of these patients. Early on, however, total LV unloading can shift the septum to the left and further exaggerate RV dilatation and reduce the septal contribution to RV function. RV failure is treated conservatively with inotropes and pulmonary vasodilators, but may require RVAD if refractory.



Figure 3-9: Impact of RV failure on outcomes after LVAD implantation. Source: Rame JE, Pagani FD, Kiernan MS, et al. Evolution of late right heart failure with left ventricular assist devices and association with outcomes. Journal of the American College of Cardiology. 2021 Dec 7;78(23):2294-308.

Prognostic factors:

Risk factors for early mortality after LVAD implantation include:

- INTERMACS profiles 1-2.

- Renal dysfunction.
- Elevated bilirubin.
- Advanced age.
- Female gender.
- Presence of right heart failure.
- Need for concomitant cardiac surgery.

Post-operative patient management:

| Table 3-4: 2019 EACTS Expert Consensus recommendations for management after LVAD implantation: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Anticoagulation: | | |
| A postoperative international normalized ratio target between 2.0 and 3.0 is recommended. | I | C |
| The use of acetylsalicylic acid (81 to 325 mg daily) is recommended ⁽¹⁾ . | I | C |
| The use of LMWH for bridging during long-term support is recommended. | I | C |
| The use of novel oral anticoagulants is not recommended. | III | B |
| Blood pressure management: | | |
| In patients with continuous-flow mechanical circulatory support, a mean systemic blood pressure goal of ≤ 85 mmHg is recommended. | I | B |
| Heart failure medication: | | |
| Heart failure medication should be considered during mechanical circulatory support. | Ila | C |

(1) The recommended dose for HeartMate II is 81-325 mg daily, while a dose of 325 mg daily is recommended for HeartWare LVAD.

Complications:

○ **Device failure:**

- Continuous-flow axial pumps: the failure of axial pumps can be catastrophic, as these pumps lack valves, which creates the equivalent of severe aortic regurgitation.
- Pulsatile pumps: failure of the pump is less catastrophic than with an axial pump, as the valves protect from severe regurgitation. However, failure of one of the valves can create the equivalent of severe AI.

○ **LVAD thrombus:** defined as the presence of a thrombus in the conduit or pump, severe haemolysis, and severe HF symptoms. When LV decompression cannot occur, the blood is pushed again through the AV, resulting in a palpable pulse. Thrombus should be suspected with the presence of hemolysis, for example, if the LDH level increases to > 1,500 or 3 times the previous level, or if there is any hemoglobinuria or significantly elevated plasma free hemoglobin.

○ **RV failure** (~20% at 2 years).

○ **Infections:** The INTERMACS report showed that infection was still the fourth most common cause of death within 1 year after implant. Driveline exit site infection is a common complication, occurring in 20-25% of patients, but the majority remain superficial and can be managed by antibiotics. Exit site swabs and blood cultures are obligatory when driveline infection is suspected.

Catheter-associated urinary tract infection is the most common nosocomial infection and is preventable by limiting the number of days of catheterization.

○ **Thromboembolic complications:** In the Heart-Mate II post-approval study, ~12% of patients had a stroke at 2 years. Thus, LVAD implants require warfarin therapy. HeartMate II requires INR 2-3.

○ **Hemorrhagic complications** (54% at 2 years), including a high risk of postoperative bleeding because of liver congestion, poor nutrition, and warfarin therapy. Also, the continuous flow may lead to arteriovenous malformations and may degrade von Willebrand factor, resulting in GI bleed. If bleeding persists, urgent heart transplant may be needed to allow withdrawal of LVAD and anticoagulation.

- **Aortic Insufficiency:** blood flows through the LVAD, bypassing the aortic valve, which remains closed and may eventually fuse. Aortic fusion leads to AI, a serious complication that may develop in up to 30% of LVAD patients at 3 years and requires AVR. Recirculating blood (AI) will lead to systemic hypoperfusion of the patient. Additionally, incomplete unloading of the LV may lead to pulmonary hypertension compromising the RV function.
- **Hemolysis** with continuous pumps.
- **Arrhythmias** such as VF. When stable LVAD patients develop VF, they feel tired but they do not develop circulatory arrest. The LV becomes fully dependent on the pump. The RV arrests but in stable patients with low PA pressure, blood flows passively through the arrested RV, similarly to a Fontan circulation. This does not apply to the early postoperative period, where the RV function is critical in surpassing the left septal pull and the high PA pressure.

Troubleshooting:

- **Causes of increased power:**

- For the same speed, an increase in power may correspond to an increase in flow. This may result from high metabolic demands or vasodilatation; in which case the pulse index is also high as the intrinsic LV flow also increases.
- An increase in power may also indicate rotor pump thrombosis; the flow reading is paradoxically and falsely increased, and the pulse index is low.

- **Causes of reduced power:** Reduced power correlates with reduced flow and indicates ↓ preload or ↑ afterload. For example, it may indicate an empty LV with a suckdown of the LV walls. It may also indicate RV failure, tamponade, inflow or outflow obstruction (kink or thrombosis), or HTN (mean BP should be kept < 90 mmHg).

- Since pulsatility is significantly attenuated with continuous-flow devices, the pulse is often not palpable and blood pressure measurement may be difficult non-invasively. An arterial Doppler is used during non-invasive BP measurement; the continuous noise heard during BP cuff deflation corresponds to mean BP. **The mean BP goal is 65-90 mmHg.**

- **In a patient with VAD, hypotension may be:**

- **VAD-related:** RV failure; VAD pump failure, malposition, or obstruction (thrombosis); LV suction or excessive pump speed.

- **Not VAD-related:** sepsis, tamponade, hemorrhage, LV suction (secondary to hypovolemia), RV failure, or high pump speed and is treated with fluid administration and slowing the pump speed.
- On echo, the septum should be kept in the middle; a septum that is excessively pulled towards the LV mandates a reduction of the LVAD speed. A dilated LV may imply LVAD pump failure.

Heart transplantation (HT)

Heart transplantation remains the gold standard for the treatment of advanced HF in the absence of contraindications. The availability of better immunosuppressive agents and other improvements in the care of HT recipients have led to dramatic increases in median survival time after HT, from several days in the beginning to 12.5 years in the current era. Furthermore, post-transplant 1-year survival has progressively increased from 84% in 1990 to 90% in 2015.

Indications:

- Advanced HF.
- No other therapeutic option, except for LVAD as BTT.

Contraindications:

- Active infection is a relative contraindication (except infected LVADs, it may actually be an indication).
- Severe peripheral arterial or cerebrovascular disease
- Pharmacologic irreversible pulmonary hypertension: The criteria for pulmonary hypertension as a contraindication for HT as recommended by the ISHLT include: pulmonary artery systolic pressure ≥ 50 mmHg and either a PVR of ≥ 3 WU or a transpulmonary gradient ≥ 15 mmHg.
If elevated pulmonary pressures are identified, a vasodilator challenge should be undertaken using intravenous vasodilator agents. If the pulmonary hypertension is reversible, then the patient is an acceptable candidate for HT, as the presence of “reversible” pulmonary hypertension does not affect posttransplant outcomes.
In those with refractory pulmonary hypertension, complete LV unloading with LVAD should be considered to reverse elevated PVR with subsequent re-evaluation to establish candidacy.
- Malignancy with poor prognosis (a collaboration with oncology specialists should occur to stratify each patient as regards their risk of tumour progression or recurrence with the use of immunosuppression).

- Irreversible liver dysfunction (cirrhosis) or irreversible renal dysfunction (e.g. creatinine clearance < 30 mL/min/1.73 m²). Combined heart-liver or heart-kidney transplant may be considered.
- Systemic disease with multiorgan involvement.
- Other serious comorbidity with poor prognosis.
- Pre-transplant BMI > 35 kg/m² (weight loss is recommended to achieve a BMI < 35 kg/m²). Size matching is an important factor affecting donor heart selection, and donor weight is recommended to be no more than 30% below that of the recipient. As a result, obese HT candidates have longer waiting times and consequently higher mortality on the wait list.
- Current alcohol or drug abuse.
- Psychological instability that jeopardizes proper follow-up and intensive therapeutic regime after HT.
- Insufficient social supports to achieve compliant care in the outpatient setting.

Notes:

- ☞ Elderly age is not an absolute contraindication. Although patients aged < 65 years might be more appropriate candidates due to their overall life expectancy, most programmes accept patients up to 70 years of age, and biological age as well as chronological age must be taken into account.
- ☞ High PVR or transpulmonary gradient, or a recently treated cancer are contraindications for HT but not for MCS. Severe renal insufficiency is a contraindication for HT, but renal or liver function may improve after MCS. On the other hand, severe RV dysfunction is a contraindication for LVAD, because there are still no good long-term solutions for RV or biventricular mechanical support.
- ☞ ABO compatibility is important but not Rh compatibility (Rh is not expressed on myocardial cells). HLA antibody assessment is recommended. Testing for preformed HLA-reactive antibodies, or panel reactive antibodies, is performed in the recipient, and is repeated after blood transfusions, as those can trigger HLA antibodies (anti-leukocytes).

Surgical Procedure:

The HT procedure requires two surgeons. One surgeon travels to the hospital where the deceased donor is located and procures the donor heart. This surgeon performs an assessment of quality of the donor heart on arrival by first reviewing the echocardiogram, hemodynamics, and coronary angiogram (if performed). If the organ is acceptable, the procurement surgery proceeds. Once the heart has been surgically exposed, the surgeon makes a final check of the coronary arteries via palpation. If there are no abnormalities, the heart is arrested using cardioplegia solution, explanted, and placed in cold storage on ice. This marks the beginning of the cold ischemic time. The procurement team then travels back to the hospital, where the recipient has already been prepared for surgery.

Upon hearing that the donor heart is acceptable, the second surgeon proceeds with the recipient cardiectomy. A sternotomy is performed. The recipient is placed on cardiopulmonary bypass, the aorta is cross-clamped and the recipient's heart is removed. Then the donor heart is brought onto the surgical field and the left atrial anastomosis is made, followed by the IVC, pulmonary artery, and aortic anastomoses. The aortic cross-clamp is released and the heart begins to be perfused with blood. It will typically start to beat spontaneously. Inotropic and vasopressor support is initiated. Then the patient is weaned from cardiopulmonary bypass. Hemostasis is achieved and the chest is closed.

Immunosuppressive therapies:

To prevent allograft rejection, HT recipients must be maintained on immunosuppressive medications for life. On the other hand, immunosuppression predisposes HT recipients to infections with typical as well as atypical pathogens. Thus, it is important in caring for HT recipients is to monitor and adjust the level of immunosuppressive medications to maintain a balance between “enough” and “too much”. The clinical approach to immunosuppression is to apply a high level of immunosuppression early after transplant and gradually decrease this level over time while monitoring for the development of allograft rejection.

- **Induction immunosuppression:** (administered shortly after HT)

The regimen includes: ***antithymocyte globulin (ATG) + interleukin-2 antagonist (Basiliximab)***. The use of induction immunosuppression is particularly important in two situations: (i) for recipients with renal dysfunction in whom induction

immunosuppression is used to delay introduction of a calcineurin inhibitor and (ii) for recipients at an elevated immunologic risk in whom induction immunosuppression is used for its long-term effects on memory T lymphocytes.

- **Maintenance regimen:**

The most common regimen used is *tacrolimus and mycophenolate mofetil (MMF) ± prednisone*.

Tacrolimus inhibit calcineurin, which is a signaling protein required for the activation and proliferation of T lymphocytes.

MMF inhibits the enzyme inosine monophosphate dehydrogenase which is required for nucleotide production, thus inhibiting T and B lymphocyte proliferation.

Corticosteroids bind to the glucocorticoid receptor, which leads to downstream changes in the expression levels of multiple genes (an increase in anti-inflammatory gene transcription and a decrease in pro-inflammatory gene transcription).

N.B:

- ☞ Sirolimus has the advantages of less cardiac allograft vasculopathy (CAV) and less renal failure than calcineurin inhibitors. Sirolimus needs to be stopped 1 week before and 4-6 weeks after elective surgery and replaced by calcineurin inhibitors to allow wound healing.
- ☞ Statin therapy started early after transplantation reduces mortality, rejection, and cardiac allograft vasculopathy. Pravastatin has the least interaction with immune suppressants.

Complications:

The two main cardiac complications of HT include allograft rejection and cardiac allograft vasculopathy.

The three main non-cardiac complications are infection, renal failure and malignancy.

- 1) Primary graft dysfunction (PGD)** is defined as the failure of graft function within the first 24 hours after transplantation in the absence of hyperacute rejection, pulmonary hypertension, or known surgical complications such as bleeding or tamponade. Dysfunction frequently manifests as hypotension, low cardiac output/index, and high filling pressures. When severe PGD is

present, the use of MCS with an IABP or ECMO is frequently needed. Even with aggressive management of PGD, mortality remains high.

2) Cardiac Allograft rejection:

- Patients with rejection present along a clinical spectrum, varying from an asymptomatic patient to a patient with fulminant cardiogenic shock. Asymptomatic patients usually come to clinical attention at the time of a surveillance EMB showing rejection, so surveillance biopsies should be performed weekly early on, then monthly up until 6 months, then every 3-6 months⁽¹⁾.
- **Clinical risk factors for rejection:** medication non-compliance, younger age of the recipient, African American ethnicity, and circulating anti-HLA antibodies. Genetic risk factors include increasing donor to recipient HLA mismatch and genetic polymorphisms within the cytokine genes.
- **The major types of rejection are:**
 - **Hyperacute rejection** occurs within minutes to hours after heart transplantation and results from *ABO incompatibility or anti-HLA antibodies*. This results in occlusion of graft vasculature and overwhelming graft failure. It is usually fatal unless treated urgently with retransplantation or mechanical support.
 - **Acute rejection** occurs most frequently in the first few months after transplant, but may occur later. It is the leading cause of death in the first month after transplant. Rejection occurs as a result of interaction between the recipient's immune system and the allograft. It may be categorized by the type of immune response (cell-mediated vs. antibody-mediated). *A clinical acute rejection is an emergency. It should be suspected in any transplant patient presenting with acute HF, especially if fever is present.* When suspected clinically, it should be treated emergently with IV steroids, even before the biopsy.
 - **Acute Cellular Rejection (ACR)** is the most common form of rejection which occurs due to direct and indirect allorecognition, which leads to T-cell activation and infiltration of the allograft. It is most common in the first 3 months, but late rejections can

(1) In contrast, a patient can present with clinical rejection and the EMB may show no evidence of rejection. This situation is termed **biopsy-negative rejection** and may be due to sampling error of the EMB or to an atypical form of AMR (e.g., non-HLA AMR).

occur. It is caught early on surveillance endomyocardial biopsies. Histopathology shows *infiltration of lymphocytes* and macrophages, with the grade of rejection corresponding to the extent of cellular infiltration and myocyte injury.

- **Antibody-mediated rejection (AMR)** is the next most common form of rejection, occurring in 9% of biopsies. AMR is due predominantly to the binding of antibodies against HLA antigens to cardiac tissue, leading to complement activation and tissue injury. Immunologically, complement components C3d or C4d are seen in a capillary pattern. Histological findings suggestive of AMR include endothelial cell activation, *intravascular macrophage* accumulation and interstitial edema.
- **Mixed rejection** where EMB displays both ACR and AMR, occurs in 8% of biopsies.
- **Treatment of rejection:**
 - If the patient displays cardiogenic shock, Inotropes should be initiated and MCS should be considered.
 - A bolus dose of steroids and ATG are administered in patients with symptomatic rejection.
 - Intravenous heparin, as coronary microvascular thrombosis occurs in severe rejection.
 - For patients with AMR: Plasma exchange and I.V immunoglobulin are frequently administered.
 - If the initial EMB shows acute rejection, EMB should be repeated 2 weeks later to confirm that the augmented immunosuppression regimen has been effective at eradicating the acute rejection.
 - For patients that do not respond fully to medical treatment, extracorporeal photopheresis is initiated.
 - For patients with no response to treatment who display fulminant graft failure, retransplantation is not advisable, as it is associated with poor outcomes in the setting of acute rejection.

3) RV failure is the second leading cause of death in the first month.

4) Cardiac allograft vasculopathy: this is a diffuse and progressive coronary arteriopathy leading to the narrowing or occlusion of the coronary arteries of the allograft due to smooth muscle cell hyperplasia and accumulation of lipids and inflammatory cells. The mechanism is both immune and non-immune (metabolic syndrome, hyperlipidemia, older age, prolonged ischemic time), and it is the leading cause of death beyond the first year of cardiac transplantation, with an estimated incidence of 8% in the first year, 30% within 5 years, and 50% within 10 years. Since it is a progressive process, the definitive treatment is eventually retransplantation. Being diffuse, the disease is underestimated by coronary angiography and is better assessed by IVUS.

Preliminary therapy consists of PCI for focal stenoses, statin, switching to sirolimus, and aggressive therapy of the metabolic syndrome. Many centers recommend yearly coronary angiography with IVUS as a screening modality.

5) Immunosuppression related side effects:

- **Infections:** The risk of death due to infection is greatest in the first year post-transplant when maximum immunosuppression is being used. Patients should be vaccinated for influenza and pneumococcal infections. Live vaccines are contraindicated. Routine prophylaxis for *pneumocystis jirovecii*, cytomegalovirus, candida, and in some cases, herpes is given to these patients.
- **Malignancy**, especially skin cancers and lymphomas. Human papillomavirus (HPV) related squamous cell cancer is the most common malignancy reported. Avoiding sun exposure is recommended in these patients. New onset of solid malignancies occurs in 10% of transplant patients after 1 to 5 years. For patients with a diagnosis of cancer, switching the calcineurin inhibitor to mTOR inhibitor may be useful.
- **Renal dysfunction**, mainly from calcineurin inhibitors.
- **Agent-specific adverse effects:** e.g., In tacrolimus: renal disease, diabetes, dyslipidemia, and metabolic derangements (hypoglycemia and hyperglycemia), fine tremor and anemia.

Notes in HT:

- ☞ Many HT recipients experience decreased physical functioning after HT as a result of several factors, including: prolonged pretransplant illness, the surgical procedure itself, high dose steroids, and cardiac denervation. The vagus nerve is cut at the time of the HT surgery and, as a result, there is initially no parasympathetic or sympathetic innervation of the transplanted heart. HT recipients experience a delayed increase in heart rate with exercise ⁽¹⁾; therefore, they frequently report fatigue with exercise.
- ☞ In patients with heart transplant, pregnancy should be discouraged in the following circumstances: first year after transplant, evidence of LV dysfunction and evidence of coronary vasculopathy.

(1) Circulating catecholamine levels rise as exercise ensues, providing a delayed chronotropic response.

In pregnancy, continue corticosteroids and calcineurin inhibitors (cyclosporine or tacrolimus), but avoid Mycophenolate mofetil. Use of azathioprine is controversial.

Important trials in Mechanical circulatory support:

| Table 3-5: Important trials in LVAD: | |
|--|--|
| Trial (date) | Summary |
| Intra-aortic balloon pump (IABP): | |
| PROTECT II (2012) | <p>Aim: To compare outcomes between Impella 2.5L and IABP in patients undergoing high-risk PCI.</p> <p>Study: 452 symptomatic patients with complex 3-vessel disease or unprotected left main coronary artery disease and severely depressed LV function were randomly assigned to IABP or Impella 2.5 support during nonemergent high-risk PCI. The primary end point was the 30-day incidence of major adverse events. A 90-day follow-up was required. The 30-day incidence of major adverse events was not different for patients with IABP or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5-supported patients at 90 days.</p> |
| IABP-SHOCK II (2012) | <p>Aim: To assess the effect of IABP on mortality in patients with AMI complicated by cardiogenic shock for whom early revascularization is planned.</p> <p>Study: 600 patients with AMI and cardiogenic shock were randomized to IABP versus no IABP. All patients received early revascularization and best available medical therapy. The use of IABP did not reduce early or late mortality.</p> |
| LVAD: | |
| LVAD vs optimal medical management: | |
| REMATCH (2001) | <p>Aim: To evaluate the efficacy of long-term LVAD (Heartmate) compared with medical management in HF patients not eligible for heart transplant.</p> <p>Study: 129 patients with end-stage heart failure who were ineligible for cardiac transplantation were randomly assigned to receive a LVAD or optimal medical management. All patients had symptoms of NYHA class IV heart failure. REMATCH trial showed improved 1-year survival in inotrope-dependent, transplant-ineligible patients with advanced HF treated with an LVAD as compared to optimal medical therapy, but 2-year survival was not statistically different. The use of LVAD in patients with advanced HF resulted in clinically meaningful survival benefit and improved quality of life.</p> |

| | |
|---|---|
| ROADMAP (2017) | <p>Aim: <i>To assess the effectiveness of the HeartMate II LVAD in ambulatory NYHA IIIB/IV HF patients who are not dependent on i.v inotropes.</i></p> <p>Study: <i>The ROADMAP trial was a prospective nonrandomized observational study of 200 patients who are not dependent on i.v inotropic support and who meet the FDA approved indications for HM II LVAD (97 with LVAD, 103 on optimal medical management). The trial showed that survival with improved functional status at 1 year was better with LVADs compared with optimal medical management.</i></p> |
| ENDURANCE (2018) | <p>Aim: <i>To evaluate the impact of blood pressure management on stroke rates in patients receiving the HeartWare LVAD System.</i></p> <p>Study: <i>465 patients with advanced HF ineligible for transplantation were randomized 2:1 to HeartMate II or control. The primary endpoint was the 12-month incidence of TIA or stroke with residual deficit 24 weeks post-event. The ENDURANCE trial failed to demonstrate noninferiority of HeartMate II versus control regarding the pre-specified primary endpoint. However, the trial confirmed that BP management is associated with reduced stroke rates in HeartMate II subjects. HeartMate II subjects, relative to control subjects, more commonly achieved the composite secondary endpoint (freedom from death, disabling stroke, and device replacement or urgent transplantation).</i></p> |
| INTREPID (2007) | <p>Aim: <i>To evaluate the impact of LVAD support on survival and quality of life in inotrope-dependent HF patients ineligible for cardiac transplantation.</i></p> <p>Study: <i>55 patients with NYHA IV symptoms who failed weaning from inotropic support were offered a Novacor LVAD. 18 of these patients did not receive an LVAD owing to patient preference or unavailability of the device but consented to follow-up and constitute a contemporaneous control group. Inotrope-dependent heart failure patients who are ineligible for transplantation have a high short-term mortality rate and derive a significant survival advantage from "destination" mechanical circulatory support.</i></p> |
| Pulsatile <u>vs</u> Axial <u>vs</u> Centrifugal flow LVAD: | |
| HeartMate -II | <p>Aim: <i>To compare continuous-flow HeartMate II with pulsatile-flow HeartMate XVE LVAD in patients with advanced HF not eligible for transplant.</i></p> |

| | |
|--------------------------|---|
| (2009) | Study: 200 patients with advanced HF who were ineligible for transplantation were randomly assigned to undergo implantation of a continuous-flow device or pulsatile-flow device. The primary composite end point was, at 2 years, survival free from disabling stroke and reoperation to repair or replace the device. Continuous-flow LVADs improve survival free from disabling stroke and device failure, as compared with pulsatile devices. |
| ADVANCE (2017) | Aim: To compare small intrapericardial centrifugal-flow against axial-flow LVAD in patients with advanced HF who were ineligible for transplant. Study: 446 patients who met contemporary criteria for LVAD implantation for permanent use were assigned, in a 2:1 ratio, to the study (centrifugal-flow device) or the control (axial-flow device). Centrifugal-flow LVAD was found to be noninferior to an axial-flow LVAD with respect to survival free from disabling stroke or device removal for malfunction or failure. |
| MOMENTUM-3 (2018) | Aim: to compare a magnetically levitated centrifugal-flow with axial-flow LVAD among HF patients requiring advanced mechanical support. Study: 366 patients with advanced heart failure were randomized to a centrifugal-flow pump versus an axial-flow pump. Patients in both groups received aspirin and warfarin (target INR 2.0-3.0) and followed to 2 years. Fully magnetically levitated centrifugal-flow LVAD was associated with less frequent need for pump replacement than an axial-flow device and was superior with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. |

References and suggested readings:

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Cardiomyopathies

General approach to Cardiomyopathy

Definition:

Cardiomyopathy is defined as 'a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality'.

Cardiomyopathy phenotypes:

- **Dilated cardiomyopathy (DCM):** DCM is defined as the presence of LV dilatation and global or regional systolic dysfunction unexplained solely by CAD or abnormal loading conditions. RV dilatation and dysfunction may be present but are not necessary for the diagnosis.
Prevalence: 0.03-0.4% in adults and 0.026% in children
- **Non-dilated left ventricular cardiomyopathy (NDLVC):** NDLVC is defined as the presence of non-ischaemic LV scarring or fatty replacement regardless of the presence of global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring.
- **Arrhythmogenic right ventricular cardiomyopathy (ARVC):** ARVC is defined as the presence of predominantly RV dilatation and/or dysfunction in the presence of histological involvement and/or electrocardiographic abnormalities in accordance with published criteria.
Prevalence: 0.08% in adults

- **Restrictive cardiomyopathy (RCM):** RCM is defined as restrictive left and/or RV pathophysiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness.
- **Hypertrophic cardiomyopathy (HCM):** HCM is defined as the presence of increased LV wall thickness (with or without RV hypertrophy) or mass that is not solely explained by abnormal loading conditions.

Prevalence: 0.2% in adults and 0.03% in children

N.B: Several forms of cardiomyopathy previously considered secondary to external factors were recently proved to have genetic contributors, leading to the '**second hit theory**', and a genetic aetiology should be kept in mind for family history taking and genetic testing.

- Alcoholic cardiomyopathy: Titin gene truncating variants (TTNtv) are present in 13.5% of patients (associated with a worse LVEF in DCM patients who consume alcohol above recommended levels).
- Cancer therapy-induced cardiomyopathy: Unrecognized rare variants in cardiomyopathy-associated genes, particularly TTNtv (in 7.5% of cases), appear to be associated with an increased risk of cancer therapy-induced cardiomyopathy.
- Peripartum cardiomyopathy: Rare truncating variants in eight genes are found in 15% of women with peripartum cardiomyopathy, and two-thirds are TTNtv (10% of patients).
- Acute myocarditis: Disease-causing variants in genes implicated in DCM, NDLVC, and ARVC have been identified in 8-22% of patients with acute myocarditis. Patients with acute myocarditis and desmosomal protein gene variants were shown to have a higher rate of recurrence and ventricular arrhythmia.

Diagnostic workup:

▪ **History and physical examination:**

- Age: For example, inherited metabolic disorders are more common in neonates and infants than in older children, whereas wild-type transthyretin amyloidosis (ATTRwt) is a disease mostly of adults > 65 years.

- History of systemic disease, toxic agents (chemotherapy, alcohol, drugs).
- Familial history of cardiac or neuromuscular disease, or sudden cardiac death ⁽¹⁾ in family members at young age (< 50 years).
Note that, the absence of familial disease does not exclude a genetic origin.
- Construction of a three- to four-generation family pedigree helps to identify Mendelian forms of inheritance and identifies other family members who may be at risk of disease development ⁽²⁾.

(1) SCDs may sometimes be reported as accidental deaths, e.g. drowning, unexplained traffic accident, and, rarely, as still-birth or sudden infant death syndromes.

(2) Most Mendelian forms of cardiomyopathy are **autosomal dominant** and are therefore characterized by the presence of affected individuals across generations, with transmission from parents of either sex (including male-to-male) and a 50% risk of allele transmission to offspring (although, due to incomplete penetrance, the proportion of affected individuals in an individual pedigree will be lower). **X-linked inheritance** should be suspected if males are the most severely affected individuals and there is no male-to-male transmission. **Autosomal recessive** inheritance, the least common pattern, is likely when both parents of the proband are unaffected and consanguineous, although severe autosomal recessive cardiomyopathies can also occur in the absence of familial consanguinity. When women - but not men-transmit the disease to children of either sex, **mitochondrial DNA variants** should be considered.

Table 4-1: Examples of signs and symptoms that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype:

Learning difficulties, developmental delay:

| | | | | |
|-------------|--------------------------|--------------------------|----------------------|-----------------|
| DCM: | - Dystrophinopathies | - Mitochondrial diseases | - Myotonic dystrophy | - FKTN variants |
| RCM: | - Noonan syndrome | | | |
| HCM: | - Mitochondrial diseases | - Noonan syndrome | - Danon disease | |

Sensorineural deafness:

| | | | | |
|-------------|--------------------------|--------------------------|--------------------|--|
| DCM: | - Epicardin variants | - Mitochondrial diseases | | |
| HCM: | - Mitochondrial diseases | - Anderson-Fabry disease | - LEOPARD syndrome | |

Visual impairment:

| | | | | |
|-------------|---|-----------------------------|--|--|
| DCM: | - CRYAB | - Type 2 myotonic dystrophy | | |
| HCM: | | | | |
| | - Mitochondrial diseases (retinal disease, optic nerve atrophy) | | | |
| | - TTR-related amyloidosis (cotton wool type vitreous opacities) | | | |
| | - Danon disease (retinitis pigmentosa) | | | |
| | - Anderson-Fabry disease (cataracts, corneal opacities) | | | |

Gait disturbance:

| | | | | |
|---------------|-------------------------|-----------------------|---------------------------|--|
| DCM: | - Dystrophinopathies | - Sarcoglycanopathies | - Myofibrillar myopathies | |
| NDLVC: | Myofibrillar myopathies | | | |
| HCM: | Friedreich ataxia | | | |

Myotonia:

| | | | | |
|-------------|--------------------|--|--|--|
| DCM: | Myotonic dystrophy | | | |
|-------------|--------------------|--|--|--|

Paraesthesia/sensory abnormalities/neuropathic pain:

| | | | | |
|-------------|-------------|--|--|--|
| RCM: | Amyloidosis | | | |
|-------------|-------------|--|--|--|

| | | | | |
|--|--------------------------------|---------------------------|----------------------|----------------------|
| HCM: | - Amyloidosis | - Anderson–Fabry disease | | |
| Carpal tunnel syndrome: | | | | |
| HCM: | TTR-related amyloidosis | | | |
| Muscle weakness: | | | | |
| DCM: | - Dystrophinopathies | - Sarcoglycanopathies | - Laminopathies | - Myotonic dystrophy |
| | - Desminopathies | | | |
| NDLVC: | - Laminopathies | - Desminopathies | | |
| RCM: | Desminopathies | | | |
| HCM: | - Mitochondrial disease | - Glycogenoses | - FHL1 variants | |
| Palpebral ptosis: | | | | |
| DCM: | - Mitochondrial diseases | - Myotonic dystrophy | | |
| HCM: | - Mitochondrial diseases | - Noonan/LEOPARD syndrome | - Myotonic dystrophy | |
| Lentigines: | | | | |
| HCM: | LEOPARD/Noonan syndrome | | | |
| Angiokeratomata: | | | | |
| HCM: | Anderson–Fabry disease | | | |
| Pigmentation of skin and scars: | | | | |
| DCM: | Haemochromatosis | | | |
| Palmoplantar keratoderma and woolly hair: | | | | |
| DCM: | - Carvajal syndrome | - DSP variants | | |
| NDLVC: | DSP variants | | | |
| ARVC: | - Naxos and Carvajal syndromes | - DSP variants | | |

- **Resting and ambulatory ECG:** Although the ECG can be normal in a small proportion of individuals with cardiomyopathy, standard ECG abnormalities are common in all cardiomyopathy subtypes and can precede the development of an overt morphological or functional phenotype by many years ⁽¹⁾.

| Table 4-2: Examples of ECG features that should raise the suspicion of specific aetiologies | |
|---|--|
| Phenotype | Finding and Specific diseases to be considered |
| DCM | AV block: <ul style="list-style-type: none"> - Laminopathy - Emery–Dreifuss 1 - Myocarditis (esp. Chagas disease, Lyme disease, diphtheria) Sarcoidosis - Desminopathy - Myotonic dystrophy Low P wave amplitude: Emery–Dreifuss 1 and 2 Atrial standstill: Emery–Dreifuss 1 and 2 Posterolateral infarction pattern: <ul style="list-style-type: none"> - Dystrophinopathy - Limb-girdle muscular dystrophy - Sarcoidosis Extremely low QRS amplitude: PLN variant |
| NDLVC | AV block: Laminopathy Desminopathy Extremely low QRS amplitude: PLN variant Low QRS voltage + atypical RBBB: Desmosomal variants |

(1) There are 5 cardiomyopathies with predilection for both VT and conduction blocks, even before overt myocardial disease: ARVD, sarcoidosis, Chagas disease, familial cardiomyopathy with lamin A/C mutation and giant-cell myocarditis.

| | |
|-------------|--|
| ARVC | T wave inversion V1-V3 + terminal activation delay ± low RV voltages ± atypical RBBB |
| RCM | AV block: - Desminopathy - Amyloidosis |
| HCM | <p>Short PR interval/pre-excitation <u>or</u> AV block:</p> <ul style="list-style-type: none"> - Amyloidosis - Anderson–Fabry disease (late stage) Danon disease - Sarcoidosis - PRKAG2 cardiomyopathy <p>Extreme LVH (Sokolow score ≥ 50):</p> <ul style="list-style-type: none"> - Danon disease - Glycogenosis (e.g. Pompe disease) - PRKAG2 cardiomyopathy <p>Low QRS voltage (or normal voltage despite increased LV wall thickness)</p> <ul style="list-style-type: none"> - Amyloidosis - Friedreich ataxia <p>Superior QRS axis ('northwest axis'): Noonan syndrome</p> <p>Q waves/pseudoinfarction pattern: Amyloidosis</p> |

▪ **Laboratory exams:**

- Routine laboratory testing aids the detection of extracardiac conditions that cause or exacerbate ventricular dysfunction (e.g. thyroid disease, renal dysfunction, and diabetes mellitus) and secondary organ dysfunction in patients with severe heart failure.
- Following specialist evaluation, additional tests to detect rare metabolic causes are often required in children, including measurement of lactate, pyruvate, pH, uric acid, ammonia, ketones, free fatty acids, carnitine profile, urine organic acids, and amino acids.

▪ **Multimodality imaging:**

- **Echocardiography:** TTE provides relevant information on global and regional RV and LV anatomy and function as well as valve function and the presence of dynamic obstruction, pulmonary hypertension, or pericardial effusions. Myocardial deformation imaging (speckle tracking or tissue Doppler) with global longitudinal strain is a more sensitive marker than EF to detect subtle ventricular dysfunction (e.g., in genotype-positive HCM, DCM, and ARVC family members), and may help discriminate between different aetiologies of hypertrophy (e.g., amyloidosis, HCM, and athlete's heart). Contrast agents can be considered for better endocardial delineation to depict the presence of hypertrabeculation, apical HCM, or apical aneurysms, and to exclude thrombus. When measuring cardiac dimensions and wall thickness in children, it is important to correct for body size, using z-scores (defined as the number of standard deviations from the population mean).
- **Cardiac MRI:** CMR combines the advantages of non-invasiveness and independence of acoustic window with the ability for tissue characterization. The latter advantage is particularly important in the diagnosis of NDLVC, ARVC, myocarditis, amyloidosis, sarcoidosis and other forms of inflammatory disease, and iron overload/ haemochromatosis. Initial evaluation should routinely include cine imaging sequences, T2-weighted sequences, pre- and post-contrast T1 mapping, and late gadolinium enhancement (LGE). When suspecting haemochromatosis, T2* mapping should be employed. Serial follow-up CMR, every 2–5 years depending on initial severity and clinical course, can assist in evaluating disease progression as well as the benefits of therapy and should be considered in all patients with cardiomyopathy.
- **Nuclear medicine** is particularly helpful in the aetiological diagnosis of cardiac amyloidosis. 18FDG-PET is useful in the identification of myocardial inflammation associated with active sarcoidosis and, potentially, in other atypical forms of myocarditis. However, a negative scan does not exclude sarcoidosis in its inactive form. In patients with HCM, DCM, and Anderson–Fabry disease, H125O or 13NH3 dipyridamole or regadenoson PET has been used to evaluate microvascular dysfunction, an important predictor of adverse outcome.
- **Cardiac CT** is primarily used in patients with a suspicion of cardiomyopathy to rule out CAD, either as an alternative diagnosis (e.g. in individuals with DCM, NDLVC, or ARVC phenotypes) or as a comorbidity affecting clinical manifestations and course. In children and adolescents, CT angiography can be useful to exclude congenital vascular malformations (e.g. anomalous left coronary artery from the pulmonary artery [ALCAPA] or anomalous pulmonary venous return).

Table 4-3: Examples of CMR tissue characterization features that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype.

| phenotype | Finding and Diseases to be considered |
|------------------|---|
| DCM | Short T2*: Haemochromatosis Subepicardial LGE: Post-myocarditis Lateral wall epicardial LGE: Dystrophinopathy Subepicardial and midwall LGE at basal septum +/- extension into inferolateral wall and RV insertion points: Sarcoidosis Apical transmural LGE: Chagas disease |
| NDLVC | Ring-like and/or subepicardial LGE pattern: DSP variants FLNC variants DES variants |
| | Septal mid-wall LGE: Laminopathy |
| ARVC | Fat and LGE (transmural RV plus sub-epicardial-midmural LV free wall): Desmosomal variants |
| RCM | Partial LV or RV apical obliteration + LGE at endocardial level: EMF/hypereosinophilia |
| HCM | Posterolateral LGE and concentric LVH Low native T1: Anderson–Fabry disease |
| | Diffuse subendocardial LGE, high native T1: Amyloidosis |
| | Patchy mid-wall in hypertrophied areas: Sarcomeric HCM |

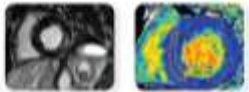
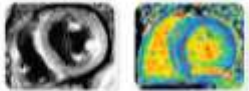










| Cardiomyopathy phenotype | Finding | Cardiac CMR examples | Specific diseases to be considered |
|--------------------------|---|---|---|
| HCM | Posterolateral LGE and concentric LVH Low native T1 |  | Anderson-Fabry disease |
| | Diffuse subendocardial LGE, high native T1 |  | Amyloidosis |
| | Patchy mid-wall in hypertrophied areas |  | Sarcomeric HCM |
| DCM | Short T2* |  | Haemochromatosis |
| | Subepicardial LGE |  | Post-myocarditis |
| | Lateral wall epicardial LGE |  | Dystrophinopathy |
| | Subepicardial and midwall LGE at basal septum +/- extension into inferolateral wall and RV insertion points |  | Sarcoidosis |
| | Apical transmural LGE |  | Chagas' disease |
| NDLVC | Ring-like and/or subepicardial LGE pattern |  | DSP variants ILNC variants DES variants |
| | Septal mid-wall LGE |  | Laminopathy |
| ARVC | Fat and LGE (transmural RV plus sub-epicardial-midmural LV free wall) |  | Desmosomal variants |
| RCM | Partial LV or RV apical obliteration + LGE at endocardial level |  | EMF/hypereosinophilia |

Figure 4-1: Examples of cardiac MRI tissue characterization features that should raise the suspicion of specific

- **Endomyocardial biopsy (EMB)** with immunohistochemical quantification of inflammatory cells and identification of viral genomes remains the gold standard for the identification of cardiac inflammation. It may confirm the diagnosis of autoimmune disease in patients with unexplained heart failure and suspected giant cell myocarditis, eosinophilic myocarditis, vasculitis, and sarcoidosis. Electron microscopy should be employed when storage or mitochondrial cardiomyopathies are suspected. EMB should be reserved for specific situations where its results may affect treatment after careful evaluation of the risk-benefit ratio.

| Table 4-4: ESC Recommendations for diagnostic work-up in cardiomyopathies: | | |
|--|--------------|--------------|
| Recommendation | Class | Level |
| <i>It is recommended that all patients with suspected or established cardiomyopathy undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging.</i> | I | C |
| <i>It is recommended that all patients with suspected cardiomyopathy undergo evaluation of family history and that a three- to four-generation family tree is created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance pattern, and identify at-risk relatives.</i> | I | C |
| Laboratory tests: | | |
| <i>Routine (first-level) laboratory tests^c are recommended in all patients with suspected or confirmed cardiomyopathy to evaluate aetiology, assess disease severity, and aid in detection of extracardiac manifestations and assessment of secondary organ dysfunction.</i> | I | C |
| <i>Additional (second-level) tests^c should be considered in patients with cardiomyopathy and extracardiac features to aid in detection of metabolic and syndromic causes, following specialist evaluation.</i> | Ila | C |
| Echocardiography: | | |

| | | |
|---|------------|----------|
| <i>A comprehensive evaluation of cardiac dimensions and LV and RV systolic (global and regional) and LV diastolic function is recommended in all patients with cardiomyopathy at initial evaluation, and during follow-up, to monitor disease progression and aid risk stratification and management.</i> | I | B |
| Cardiac MRI: | | |
| <i>Contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation.</i> | I | B |
| <i>Contrast-enhanced CMR should be considered in patients with cardiomyopathy during follow-up to monitor disease progression and aid risk stratification and management.</i> | IIa | C |
| <i>Contrast-enhanced CMR should be considered for the serial follow-up and assessment of therapeutic response in patients with cardiac amyloidosis, Anderson-Fabry disease, sarcoidosis, inflammatory cardiomyopathies, and haemochromatosis with cardiac involvement.</i> | IIa | C |
| <i>In families with cardiomyopathy in which a disease-causing variant has been identified, contrast-enhanced CMR should be considered in genotype-positive/phenotype-negative family members to aid diagnosis and detect early disease.</i> | IIa | B |
| <i>In cases of familial cardiomyopathy without a genetic diagnosis, contrast-enhanced CMR may be considered in phenotype-negative family members to aid diagnosis and detect early disease.</i> | IIb | C |
| CT and nuclear imaging: | | |
| <i>DPD/PYP/HMDP bone-tracer scintigraphy is recommended in patients with suspected ATTR-related cardiac amyloidosis to aid diagnosis.</i> | I | B |

| | | |
|---|------------|----------|
| <i>Contrast-enhanced cardiac CT should be considered in patients with suspected cardiomyopathy who have inadequate echocardiographic imaging and contraindications to CMR.</i> | Ila | C |
| <i>In patients with suspected cardiomyopathy, CT-based imaging should be considered to exclude congenital or acquired coronary artery disease as a cause of the observed myocardial abnormality.</i> | Ila | C |
| <i>18F-FDG-PET scanning should be considered for the diagnostic work-up in patients with cardiomyopathy in whom cardiac sarcoidosis is suspected.</i> | Ila | C |
| Endomyocardial biopsy: | | |
| <i>In patients with suspected cardiomyopathy, EMB should be considered to aid in diagnosis and management when the results of other clinical investigations suggest myocardial inflammation, infiltration, or storage that cannot be identified by other means.</i> | Ila | C |

▪ **Genetic testing and counselling:**

Table 4-5: Utility of genetic testing in cardiomyopathies:

For the Index patient:

- **Diagnosis:** for the affected individual, the diagnosis of cardiomyopathy is primarily made on the basis of a phenotypic definition of disease, without reference to genetic aetiology. However, with appropriate genetic counselling and acknowledging the caveat that the finding will only be clinically actionable when a P/LP variant is found, genetic testing may be of value in clarifying borderline cases (e.g. where LVH is observed in the context of mild or controlled hypertension, but the clinician is not able to confidently distinguish between early sarcomeric HCM and a hypertensive phenocopy). Genetic testing can also identify genocopies: distinct genetic conditions that mimic a particular cardiomyopathy.

- **Prognosis:** for an increasing number of conditions, a genetic diagnosis can provide prognostic information. For example, DCM due to variants in LMNA has an adverse prognosis requiring more frequent surveillance with a lower threshold for primary prevention ICD implantation.
- **Therapy:** a genetic diagnosis may directly stratify choice of therapy. In addition to decisions on primary prevention ICD implantation, an increasing number of treatments are either established or under trial for a specific molecular subtype of cardiomyopathy. In addition, further waves of therapies aiming to replace, alter, or remove abnormal genes and transcripts responsible for cardiomyopathies are anticipated once a precise molecular aetiology is established in a patient.
- **Reproductive advice:** a genetic diagnosis informs reproductive advice and management for an affected adult and/or the parents of an affected child, enabling tailored advice on inheritance patterns and the risk of transmission to future children.

For relatives:

Cardiomyopathies display incomplete and age-related penetrance, with great variability ⁽¹⁾, therefore it is very difficult to identify clinically those relatives who are not at risk of developing cardiomyopathy. Genetic testing of Mendelian cardiomyopathy genes has become a standard aspect of clinical management in affected families. First-line testing should be focused on genes robustly associated with the presenting phenotype.

- If initial testing does not reveal a cause, but suspicion of a monogenic cause remains high, then more extended sequencing or analysis may be indicated.

(1) *Cardiomyopathies are characterized by a marked genetic and allelic heterogeneity, that is, many different variants in many different genes can cause the same phenotype. Rare pathogenic variants associated with cardiomyopathies often exhibit the phenomena of incomplete and age-related penetrance, and variable expressivity. That is, not all individuals carrying a causative variant manifest the disease and, among those who do, there is broad variability in age of onset and disease severity. Thus, while some individuals may have severe disease necessitating cardiac transplantation at a young age, others may remain unaffected throughout their lives or are only mildly affected.*

- Once a genetic cause is established in one family member, then other family members may undergo testing for only the causative variant.
- In a scenario where a first-degree relative has died, evaluation of close relatives of the deceased individual (i.e., second-degree relatives of the index patient) should also be considered.
- Individuals who are found not to harbour the familial variant can usually be discharged from clinical follow-up; those who do carry the familial variant are recommended to undergo clinical evaluation.

| Table 4-6: ESC Recommendations for genetic counselling and testing in cardiomyopathies: | | |
|--|-------|-------|
| Recommendation | Class | Level |
| Genetic counselling: | | |
| Genetic counselling is a process that aims to support patients and their families to understand and adapt to the medical, psychosocial, and familial impact of genetic diseases. | | |
| <i>Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.</i> | I | B |
| <i>It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.</i> | I | B |
| <i>Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.</i> | I | B |

| | | |
|---|------------|----------|
| <i>If pre-natal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.</i> | I | C |
| <i>A discussion about reproductive genetic testing options with an appropriately trained healthcare professional should be considered for all families with a genetic diagnosis.</i> | IIa | C |
| Index patients: | | |
| <i>Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.</i> | I | B |
| <i>Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at post-mortem if a genetic diagnosis would facilitate management of surviving relatives.</i> | I | C |
| <i>Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives.</i> | IIb | C |
| <i>Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams.</i> | IIb | C |
| Family members: | | |

| | | |
|---|------------|----------|
| <i>It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).</i> | I | B |
| <i>Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences.</i> | IIa | B |
| <i>Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence.</i> | IIa | C |
| <i>Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family.</i> | III | C |

Diagnostic approach to paediatric patients:

Paediatric-onset cardiomyopathies often represent two opposite ends of the spectrum of heart muscle disease: **(i)** severe, early-onset disease, with rapid disease progression and poor prognosis, in keeping with the most severe presentations in adults; or **(ii)** early phenotypic expression of adult cardiomyopathy phenotypes, increasingly identified as a result of family screening. In infants, symptoms and signs of heart failure include tachypnoea, poor feeding, excessive sweating, and failure to thrive.

Because the NYHA classification to grade heart failure is not applicable to children under the age of 5 years, the Ross Heart Failure classification has been adopted in children < 5 years of age but has not been validated against outcomes.

- **In infants with DCM**, we should consider:
 - reversible causes (i.e. hypocalcaemic vitamin D-dependent rickets) and
 - CHD (aortic coarctation and ALCAPA, requiring immediate surgical management).
 - Viral myocarditis may be assessed by non-invasive and invasive (EMB) investigations, in selected cases.
 - Neuromuscular (dystrophin- and sarcoglycan-related cardiomyopathies) should be excluded in patients presenting with muscle hypotonia and increased CK.
 - When a DCM phenotype is associated with LV hypertrabeculation, other mitochondrial/metabolic diseases, including Barth syndrome, should be considered.
- **ARVC and NDLVC** phenotypes are very rare in infants, and are most commonly autosomal recessive forms associated with cutaneous manifestations (e.g. Naxos disease and Carvajal syndrome). Recent data suggest that ~15% of ARVC patients present with paediatric-onset disease and paediatric ARVC patients more often present with severe phenotype and higher risk of SCD.
- **Isolated RCM** is rare in infants, but a mixed RCM/HCM phenotype is more frequently encountered.
- **In infants with HCM**, we should consider:
 - Reversible causes (e.g., maternal diabetes, twin–twin syndrome, corticosteroid use).
 - Early-onset sarcomeric disease even in the absence of a family history for HCM and SCD; these infants present with severe heart failure symptoms, and survival beyond the first year of life is uncommon.
 - Malformation syndromes or metabolic disorders, in whom survival rates are <90% and <70% at 1 year, respectively.
 - In infants with HCM, biventricular hypertrophy, often presenting with signs of heart failure and systolic dysfunction, and ≥ 1 red flag for metabolic disease (muscle hypotonia, increased CK, and transaminases, consanguinity or matrilineal pattern of inheritance), it is mandatory to exclude inborn errors of metabolism, including glycogenosis type II (Pompe disease), fatty acid oxidation defects, and mitochondrial disorders.

- In infants with HCM, in the presence of biventricular outflow tract obstruction and ≥ 1 red flag for a neurocardiofaciocutaneous syndrome (dysmorphisms, cutaneous abnormalities, skeletal anomalies, etc.), a diagnosis of RASopathies should be strongly suspected.

Severe LVOTO in RASopathy-related HCM often requires high-dose beta blockade and, in some cases, consideration of septal myectomy.

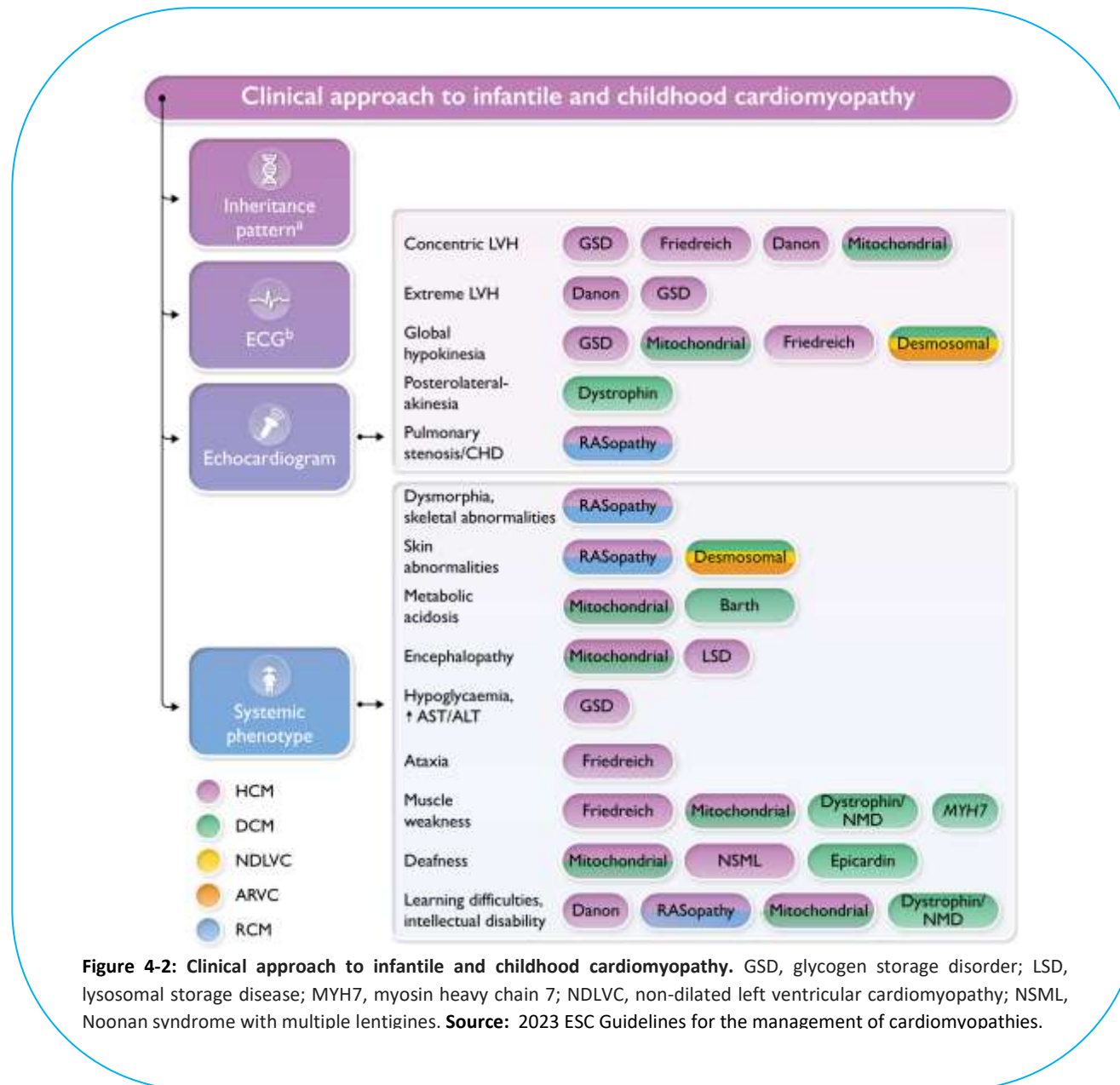


Figure 4-2: Clinical approach to infantile and childhood cardiomyopathy. GSD, glycogen storage disorder; LSD, lysosomal storage disease; MYH7, myosin heavy chain 7; NDLVC, non-dilated left ventricular cardiomyopathy; NSML, Noonan syndrome with multiple lentigines. **Source:** 2023 ESC Guidelines for the management of cardiomyopathies.

Management strategy:

- **Heart failure management:**

- Medical therapies for HFrEF including ACE-I/ARNIs, beta-blockers, MRA, and SGLT2i, would be mostly applicable to genetic DCM, NDLVC, and other phenotypes associated with LV dysfunction (e.g. end-stage HCM, RCM, and ARVC). Indications for a CRT device would be generally applicable.
- Recommendations for management of HFpEF would be mainly applicable to non-obstructive HCM, RCM, and cardiac amyloidosis.
- Cardiac amyloidosis and some forms of RCM deserve special consideration regarding heart failure management. Fluid control and maintenance of euvolaemia are central.
- Orthotopic cardiac transplantation should be considered in patients with moderate-to-severe drug-refractory symptoms (NYHA III–IV) who meet standard eligibility criteria. This may include patients with RCM and HCM with normal LVEF but severe drug-refractory symptoms caused by diastolic dysfunction.
- Mechanical circulatory support with an LVAD or biventricular assist device is increasingly used as a bridge to transplant, or as destination therapy.

| Table 4-7: ESC Recommendations for the management of HF symptoms in patients with cardiomyopathy: | | |
|---|-------|-------|
| Recommendation | Class | Level |
| Heart transplant: | | |
| <i>Orthotopic cardiac transplantation is recommended for eligible cardiomyopathy patients with advanced heart failure (NYHA class III–IV) or intractable ventricular arrhythmia refractory to medical/invasive/ device therapy, and who do not have absolute contraindications.</i> | I | C |
| Left Ventricular assist device: | | |
| <i>Mechanical circulatory support therapy should be considered in selected cardiomyopathy patients with advanced heart failure (NYHA class III–IV) despite optimal pharmacological and</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>device treatment, who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of heart failure hospitalization from worsening heart failure and premature death while awaiting a transplant.</i> | | |
| <i>Mechanical circulatory support therapy should be considered in selected cardiomyopathy patients with advanced heart failure (NYHA class III–IV) despite optimal pharmacological and device therapy, who are not eligible for cardiac transplantation or other surgical options, and without severe right ventricular dysfunction, to reduce the risk of death and improve symptoms.</i> | Ila | B |

- **Management of atrial fibrillation:**

- Atrial fibrillation is the most common arrhythmia in all subtypes of cardiomyopathies and is associated with an increased risk of cardio-embolic events, heart failure, and death.
- Thrombo-embolic risk varies in different cardiomyopathy phenotypes. Cardiac amyloidosis, HCM, and RCM are associated with a particularly increased risk of stroke. For this reason, prophylactic anticoagulation is recommended in all patients with AF and HCM, RCM or cardiac amyloidosis.
- Rate control should be considered in any patient with cardiomyopathy presenting with AF. lenient rate control (resting heart rate < 110 b.p.m.) is acceptable as an initial approach but to target a lower heart rate in case of persistent symptoms or suspicion of associated tachycardia-induced cardiac dysfunction. Beta-blockers are the preferred choice in patients with cardiomyopathies given their long-established safety in the presence of LV dysfunction.
- Atrial fibrillation can result in haemodynamic and clinical decompensation due to shortening of the diastolic filling time with rapid heart rates and dependence on atrial contraction for LV filling. Therefore, maintenance of sinus rhythm is highly desirable and a rhythm control strategy is preferred, particularly in the presence of symptoms.

| Table 4-8: ESC Recommendations for management of AF and A flutter in patients with cardiomyopathy: | | |
|---|---------------------|---------------------|
| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |

| | | |
|---|------------|----------|
| Anticoagulation: | | |
| <i>Oral anticoagulation in order to reduce the risk of stroke and thrombo-embolic events is recommended in all patients with HCM or cardiac amyloidosis and AF or atrial flutter (unless contraindicated).</i> | I | B |
| <i>Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events is recommended in patients with DCM, NDLVC, or ARVC, and AF or atrial flutter with a CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women.</i> | I | B |
| <i>Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events should be considered in patients with RCM and AF or atrial flutter (unless contraindicated).</i> | IIa | C |
| <i>Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events should be considered in patients with DCM, NDLVC, or ARVC, and AF or atrial flutter with a CHA2DS2-VASc score of 1 in men or of 2 in women.</i> | IIa | B |
| Control of symptoms and heart failure: | | |
| <i>Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III AAD to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy.</i> | I | B |
| <i>Atrial fibrillation catheter ablation is recommended to reverse LV dysfunction in AF patients with cardiomyopathy when tachycardia-induced component is highly probable, independent of their symptom status.</i> | I | B |
| <i>Maintenance of sinus rhythm rather than rate control should be considered at an early stage for patients with a cardiomyopathy and AF without major risk factors for recurrence, regardless of symptoms.</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>Atrial fibrillation catheter ablation should be considered as first-line rhythm control therapy to improve symptoms in selected patients with cardiomyopathy and paroxysmal or persistent AF without major risk factors for recurrences as an alternative to class I or III AADs, considering patient choice, benefit, and risk.</i> | Ila | C |
| <i>Atrial fibrillation catheter ablation should be considered in selected patients with cardiomyopathy, AF, and heart failure and/or reduced LVEF to prevent AF recurrences and improve QoL, LVEF, and survival and reduce heart failure hospitalization.</i> | Ila | B |
| Comorbidities and associated risk factors management: | | |
| <i>Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity in patients with cardiomyopathy.</i> | I | B |

- **Management of ventricular arrhythmias and ICD:**

- Any reversible cause and/or precipitating factor, such as electrolyte imbalances, ischaemia, hypoxaemia, or drugs, should be identified and corrected when possible.
- Extensive efforts should be made to understand the aetiology (i.e. underlying mechanism and substrate) as this will influence the choice of treatment.
- Acute termination of sustained ventricular arrhythmias can be achieved with electrical cardioversion, AADs, or pacing. The initial choice of treatment will depend on the haemodynamic tolerance, the underlying aetiology, and the patient profile.
- In patients with cardiomyopathies and scar-related ventricular arrhythmias, the therapeutic arsenal for long-term prevention of recurrent ventricular arrhythmias includes antiarrhythmic medications (mostly limited to beta-blockers, sotalol, and amiodarone) and catheter ablation (particularly in the case of sustained monomorphic VT or in the case of polymorphic VT triggered by a PVC of similar morphology).

- Additional strategies may be considered, depending on the characteristics of the patient and the ventricular arrhythmia, including acute neuromodulation strategies (stellate ganglion block and thoracic epidural anaesthesia), chronic neuromodulation strategies (cardiac sympathetic denervation), and stereotactic non-invasive VT ablation.
- ICD reduces mortality in survivors of cardiac arrest and in patients who experienced haemodynamically compromising sustained ventricular arrhythmias. An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should consider the patient's view and their QoL, as well as the absence of other diseases likely to cause death within the following year.

Table 4-9: ESC Recommendations for ICD in patients with cardiomyopathy:

| Recommendation | Class | Level |
|---|--------------|--------------|
| General recommendations: | | |
| <i>Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good quality survival > 1 year.</i> | I | C |
| <i>It is recommended that ICD implantation be guided by shared decision-making that:</i> <ul style="list-style-type: none"> - <i>Is evidence-based;</i> - <i>Considers a person's individual preferences, beliefs, circumstances, and values; and</i> - <i>ensures that the person understands the benefits, harms, and possible consequences of different treatment options</i> ⁽¹⁾. | I | C |
| <i>It is recommended that prior to ICD implantation, patients are counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device.</i> | I | C |
| <i>It is not recommended to implant an ICD in patients with incessant ventricular arrhythmias until the ventricular arrhythmia is controlled.</i> | III | C |

(1) Shared decision-making is greatly enhanced by patient decision aids tailored specifically to receivers of care as well as more traditional decision-support tools for healthcare practitioners.

| | | |
|---|-----|---|
| Secondary prevention: | | |
| Implantation of an ICD is recommended in patients with ⁽¹⁾ : | | |
| - HCM, DCM, and ARVC who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes. | I | B |
| - NDLVC and RCM who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes. | I | C |
| ICD implantation should be considered in patients with cardiomyopathy presenting with haemodynamically tolerated VT, in the absence of reversible causes. | Ila | C |
| Primary prevention: | | |
| Comprehensive SCD risk stratification is recommended in all cardiomyopathy patients who have not suffered a previous cardiac arrest/sustained ventricular arrhythmia at initial evaluation and at 1–2 year intervals, or whenever there is a change in clinical status. | I | C |
| The use of validated SCD algorithms/scores as aids to the shared decision-making when offering ICD implantation, where available ⁽²⁾ : | | |
| - is recommended in patients with HCM. | I | B |
| - should be considered in patients with DCM, NDLVC, and ARVC. | Ila | B |
| If a patient with cardiomyopathy requires pacemaker implantation, comprehensive SCD risk stratification to evaluate the need for ICD implantation should be considered. | Ila | C |
| Choice of ICD: | | |
| When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from CRT. | I | A |

(1) The difference in level of evidence reflects the different levels of evidence available for the various cardiomyopathy phenotypes.

(2) The difference in class of recommendation reflects different performance of available models for different cardiomyopathy phenotypes.

| | | |
|---|------------|----------|
| <i>Subcutaneous defibrillators should be considered as an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia, cardiac resynchronization, or antitachycardia pacing is not anticipated.</i> | Ila | B |
| <i>The wearable cardioverter defibrillator should be considered for adult patients with a secondary prevention ICD indication who are temporarily not candidates for ICD implantation.</i> | Ila | C |

- **Routine follow-up of patients with cardiomyopathy:**

| Table 4-10: ESC Recommendations for routine follow-up of patients with cardiomyopathy: | | |
|--|--------------|--------------|
| Recommendation | Class | Level |
| <i>It is recommended that all clinically stable patients with cardiomyopathy undergo routine follow-up using a multiparametric approach that includes ECG and echocardiography every 1 to 2 years.</i> | I | C |
| <i>Clinical evaluation with ECG and multimodality imaging is recommended in patients with cardiomyopathy whenever there is a substantial or unexpected change in symptoms.</i> | I | C |

Family screening and follow-up evaluation of relatives:

- All first-degree relatives of patients with cardiomyopathy should be offered clinical screening with ECG and cardiac imaging (echocardiogram [ECHO] and/or CMR).
- In families in whom a disease-causing genetic variant has been identified, cascade genetic testing should be offered:
 - Individuals found not to carry the familial variant and who do not have a clinical phenotype can be discharged, with re-assessment in presence of symptoms or new clinically relevant data in the family.

- Those relatives harbouring the familial genetic variant(s) should undergo regular clinical evaluation with ECG, multimodality cardiac imaging, and additional investigations (e.g. Holter monitoring).
- Cardiac screening in: (i) carriers of genetic P/LP variants associated with cardiomyopathies; or (ii) in those with demonstration of a familial disease should be offered from childhood to old age.

The proposed frequency of screening is every 1–3 years with ECG and ECHO (plus additional tests where this is considered appropriate) before the age of 60 years, and then every 3–5 years thereafter.

- If a genetic cause of the disease has not been identified, either because P/LP variants are absent in the proband or because genetic testing has not been performed, clinical follow-up of all first-degree relatives is recommended.
- Disease-penetrance studies have demonstrated a similar sigmoid shape pattern of phenotypic expression throughout life in families with confirmed genetic cardiomyopathies. The penetrance during childhood is ~5% during the first decade of life, increasing to 10–20% per decade from the second to the seventh decades, after which the slope flattens to 5–10% in the last decades. Penetrance in most cardiomyopathies is incomplete, reaching 70–90% by the age of 70 years.

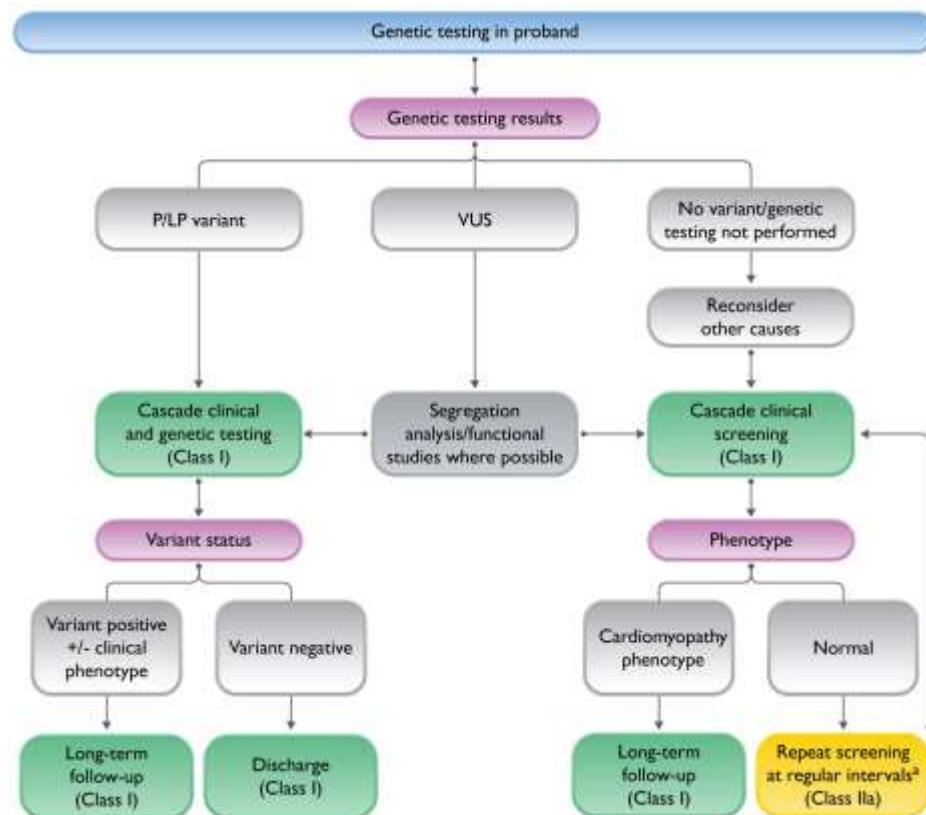


Figure 4-3: Algorithm for the approach to family screening and follow-up of family members. P/LP, pathogenic/likely pathogenic, VUS, variant of unknown significance. If no additional affected relatives and no variant identified on genetic testing, consider earlier termination of clinical screening. **Source:** 2023 ESC Guidelines for the management of cardiomyopathies.

Table 4-11: ESC Recommendations for family screening and follow-up evaluation of relatives:

| Recommendation | Class | Level |
|----------------|-------|-------|
|----------------|-------|-------|

| | | |
|---|------------|----------|
| <i>Following cascade genetic testing, clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging and long-term follow-up is recommended in first-degree relatives who have the same disease-causing variant as the proband.</i> | I | B |
| <i>Following cascade genetic testing, it is recommended that first-degree relatives without a phenotype who do not have the same disease-causing variant as the proband are discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.</i> | I | C |
| <i>It is recommended that when no P/LP variant is identified in the proband or genetic testing is not performed, an initial clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging is performed in first-degree relatives.</i> | I | C |
| <i>When no P/LP variant is identified in the proband or genetic testing is not performed, regular, long-term clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging should be considered in first-degree relatives.</i> | IIa | C |
| <i>During cascade screening, where a first-degree relative has died, clinical evaluation of close relatives of the deceased individual (i.e. second-degree relatives of the index patient) should be considered.</i> | IIa | C |

| | | |
|---|--|--|
| | | |
| Hypertrophic cardiomyopathy | Dilated cardiomyopathy | Arrhythmogenic cardiomyopathy |
| Prevalence | | |
| ≈1:500 | ≈1:250 | ≈1:5000 to 1:2000 |
| Typical Clinical Presentation | | |
| Age at presentation: 25-40 years Symptoms: syncope, exercise intolerance, palpitations, dyspnea, SCA or SCD | Age at presentation: 20-50 years Symptoms: fatigue, dyspnea, dizziness, exercise intolerance, SCA or SCD | Age at diagnosis: 20-45 years Symptoms: syncope, palpitations, dyspnea, SCA or SCD |
| Diagnosis | | |
| Methods: Echocardiography, CMR Criteria: LV wall thickness of ≥15 mm* LVOTO = peak LVOT pressure gradient ≥30 mm Hg | Methods: Echocardiography or CMR Criteria: unexplained LVEF <50% | Methods: ECG, Echocardiography, CMR, SAECG, Holter monitoring, FHx, genetic test, EMB Criteria: revised Task Force criteria |
| Risk Factors for Sudden Cardiac Death | | |
| <ul style="list-style-type: none"> • unexplained syncope • NSVT • LVOTO ≥50 mm Hg • FHx of SCD <40 years and/or HCM-SCD • LVH ≥30 mm • extensive LGE | <ul style="list-style-type: none"> • LVEF • age at diagnosis • LMNA, FLNC, DSP, PLN, or RBM20 mutation • LGE • T-Wave alternans | <ul style="list-style-type: none"> • male sex • age at diagnosis • cardiac syncope • Number of leads with TWI • ↑PVC count/24 hour • NSVT • ↓RVEF |
| Mortality | | |
| Annual SCD mortality: ≈1% Annual mortality: ≈3% | Annual SCD mortality: ≈2-3% Annual mortality: ≈5-6% | Annual rate of VT/VF/SCD: ≈2-3% Annual mortality: ≈1% |
| Genetics | | |
| Genetic test diagnostic yield: ≈65% Affected structures: cardiac sarcomere Common genes: MYH7, MYBPC3 | Genetic test diagnostic yield: ≈30-35% Affected structures: diverse structures Common genes: TTN, LMNA, MYH6, SCN5A | Genetic test diagnostic yield: ≈65% Affected structures: cardiac desmosome Common genes: PKP2, DSP, DSG2, PLN |
| Implications of Genetic Testing | | |
| Diagnostic: no Risk stratification: no Management: no Presympt. diagnosis in the family: yes | Diagnostic: no Risk stratification: yes Management: yes Presympt. diagnosis in the family: yes | Diagnostic: no Risk stratification: no Management: no Presympt. diagnosis in the family: yes |
| Management | | |
| Drug therapy: β-blockers or non-DHP CCB disopyramide Interventional: septal ablation (HOCM) Surgery: septal myectomy (HOCM) Cardiac device: ICD in high-risk patients | Drug therapy: standard therapy for HF Cardiac device: ICD or CRT-P/D in high-risk patients | Drug therapy: β-blockers HF therapy (if indicated) Cardiac device: ICD in high-risk patients |

Figure 4-4: The Clinical and Genetic Characteristics of Hypertrophic, Dilated, and Arrhythmogenic Cardiomyopathies.
*In the presence of family history of HCM, left ventricular wall thickness of ≥ 13 mm is diagnostic for HCM. CRT-P/D =

Dilated Cardiomyopathy (DCM)

Diagnosis:

- **Index case:** DCM is defined as the presence of LV dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions (e.g. hypertension, valve disease, CHD) or CAD.

LV dilatation is defined as LV end-diastolic diameter > 58 mm in males and > 52 in females and an LVEDV index of $\geq 75 \text{ mL/m}^2$ in males and $\geq 62 \text{ mL/m}^2$ in females by ECHO.

Very rarely, LV dilatation can occur with normal LVEF in the absence of athletic remodelling or other environmental factors; this is not in itself a cardiomyopathy, but may represent an early manifestation of DCM. The preferred term for this is ***isolated LV dilatation***.

- **In relatives:** Clinical testing in relatives often reveals mild non-diagnostic abnormalities. In this context, a diagnosis of DCM in a relative is done by: **(i)** the presence of a familial causative variant, or **(ii)** the presence of isolated LV dilatation with preserved systolic function.

In the absence of conclusive genetic information in a family, DCM is considered familial if: **(i)** one or more first- or second-degree relatives have DCM; or **(ii)** when an otherwise unexplained SCD has occurred in a first-degree relative at any age with an established diagnosis of DCM.

Causes:

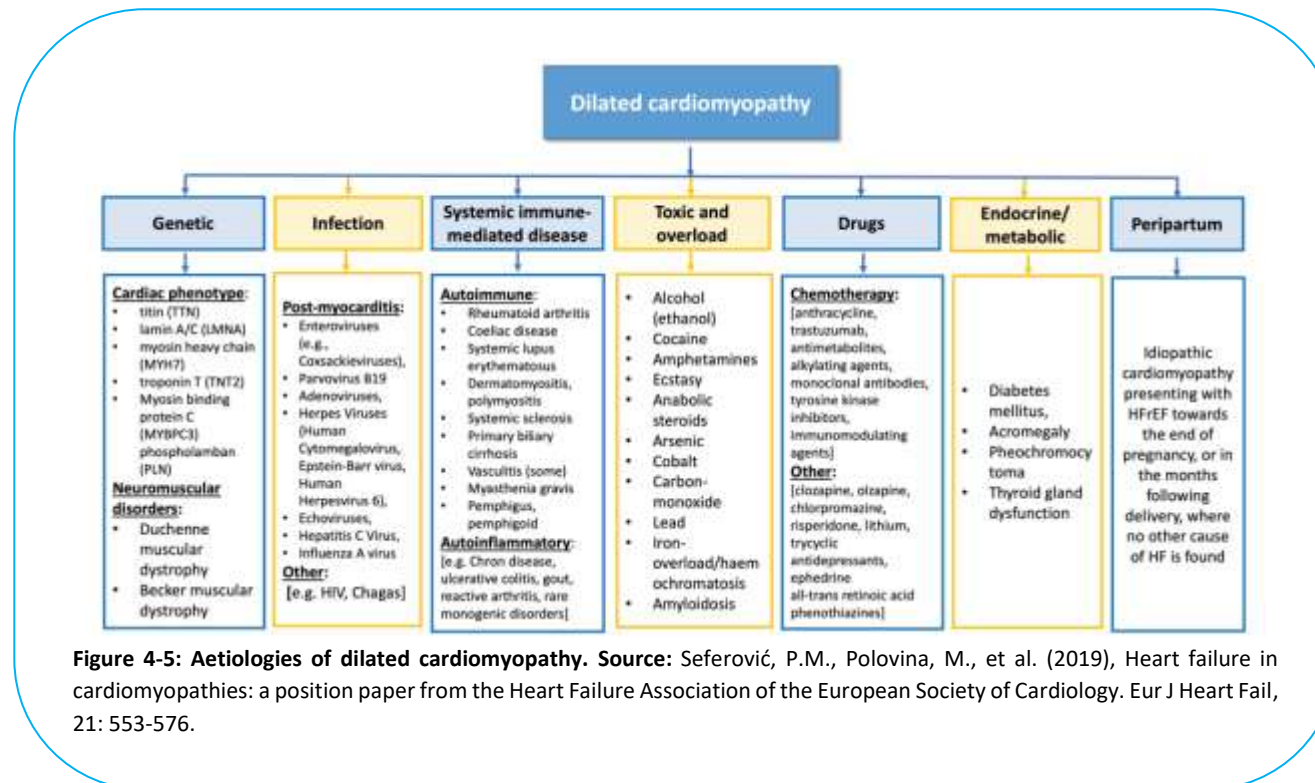


Figure 4-5: Aetiologies of dilated cardiomyopathy. Source: Seferović, P.M., Polovina, M., et al. (2019), Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail, 21: 553-576.

Genetic testing:

- The aetiology of DCM is heterogeneous and includes inherited (genetic/familial) and acquired causes. It is important to consider the interplay between genetic and acquired causes. Identification of an acquired cause does not exclude an underlying causative gene variant, whereas the latter may require an additional acquired cause and/or disease modifier to manifest.
- Causative gene variants occur in up to 40% of DCM patients (most often autosomal dominant), and between 10 and 15% in chemotherapy-induced, alcoholic, or peripartum DCM.

- Monogenic gene variants causing DCM are highly heterogeneous, implicating many genes and diverse pathways. There are genes robustly associated with classical DCM, and also others classically associated with ARVC but that very commonly can present with LV dilatation and predominantly LV dysfunction. Moreover, genes described in the context of hypertrabeculation/LVNC (e.g. NKX2.5 and PRDM16), or that can cause DCM with or without skeletal involvement (such as DMD or EMD), should also be considered DCM-associated genes and examined, particularly if phenotype is concordant.

Sudden cardiac death prevention:

- SCD occurs in up to 12% of patients with DCM and still accounts for 25-35% of all deaths.
- **SCD predictors in DCM:** LVEF, NYHA class, LGE on CMR and pathogenic mutations in LMNA, PLN, FLNC, DSP, and RBM20. Carriers of desmosomal and LMNA variants experienced the highest rate of VA/SCD.
- **LMNA mutations:** represent 5-10% of all DCM patients. LMNA mutations are associated with early atrial and ventricular arrhythmias, premature conduction disease, a high risk of SCD, and progression to end-stage heart failure. VA occurred only in persons with at least two of the following risk factors: NSVT, LVEF < 45%, male sex, non-missense mutations and AV block.
- **Secondary prevention of SCD:** ICD implantation is recommended in patients with DCM who survive SCA due to VT/VF or experience haemodynamically not-tolerated SMVT. Despite the lack of data, ESC guidelines recommend that ICD should also be considered in case of haemodynamically tolerated VT.
- **Primary prevention of SCD:** Re-evaluation of cardiac function and clinical status after 3 months' OMT is required before primary prevention ICD implantation.
 - In patients with LVEF ≤35%: While a trial including both ischaemic and non-ischaemic symptomatic heart failure patients showed reduction in mortality, trials including only patients without CAD did not significantly improve the overall risk of mortality despite the fact that there was an absolute reduction in SCD with ICDs.
 - In patients without a high-risk genotype and LVEF > 35%, multiple risk factors may help guide ICD implantation. These factors include: such as syncope or the presence of NSVT and burden of ventricular ectopy, and the presence and extent of myocardial scarring determined by LGE on CMR imaging.

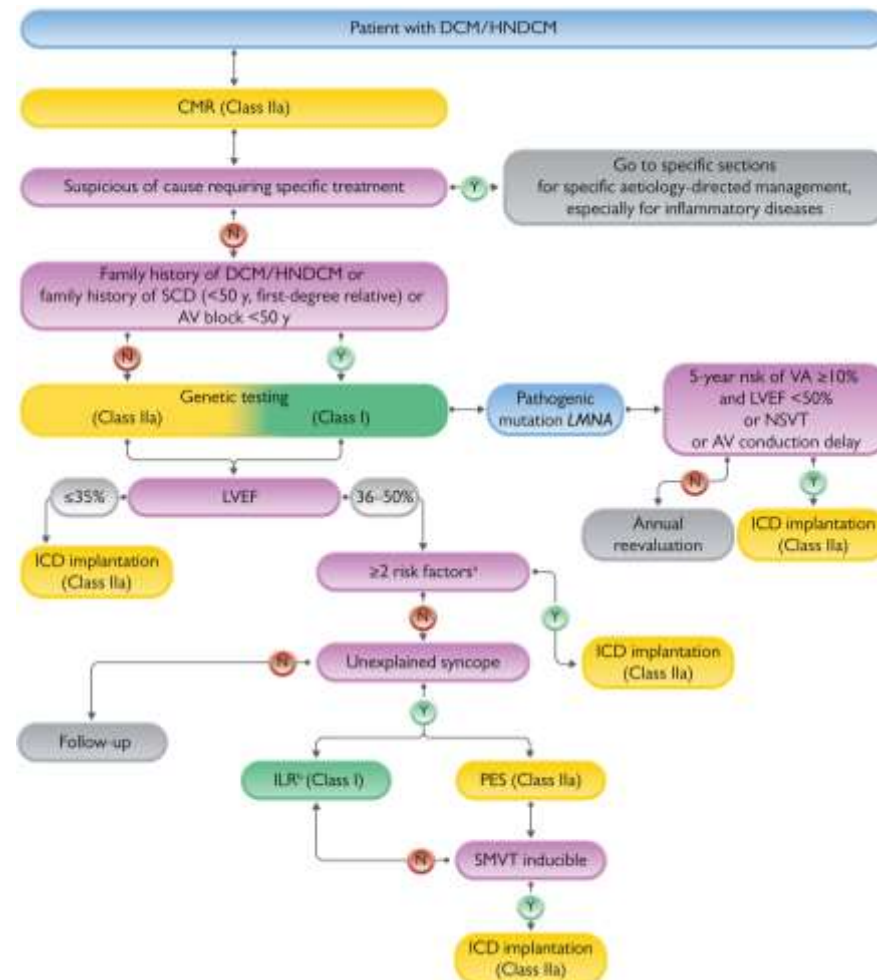


Figure 4-6: Algorithm for risk stratification and primary prevention of sudden cardiac death in patients with DCM/NDLVC. (A) Risk factors: unexplained syncope, pathogenic variants in PLN, FLNC, or RBM20, LGE on CMR, inducible SMVT at PES. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 4-12: ESC Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in DCM/NDLVC:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Diagnostic evaluation and general recommendations: | | |
| <i>In patients with DCM/NDLVC, Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes)</i> <i>- is recommended in patients with AV conduction delay at < 50 years, <u>or</u> who have a family history of DCM/NDLVC or SCD in a first-degree relative (at age < 50 years).</i> <i>- should be considered for risk stratification in patients who present at young age, <u>or</u> with signs suspicious for an inherited aetiology</i> | I | B |
| | Ila | C |
| <i>CMR with LGE should be considered in DCM/NDLVC patients for assessing the aetiology and the risk of VA/SCD.</i> | Ila | B |
| <i>Moderate- and high-intensity exercise should be considered in individuals who are gene positive and phenotype negative (with the exception of pathogenic variants in LMNA and TMEM43) who seek to do so.</i> | Ila | C |
| <i>High-intensity exercise and competitive sport may be considered in a select group of asymptomatic and optimally treated individuals with a LVE \geq 50% in the absence of exercise-induced complex arrhythmias.</i> | Ilb | C |
| <i>Moderate-intensity exercise may be considered in asymptomatic and optimally treated individuals with a left ventricular ejection fraction of 40–49% in the absence of exercise-induced complex arrhythmias.</i> | Ilb | C |
| <i>High-intensity exercise, including competitive sport, is not recommended in symptomatic individuals, those with a LVEF \leq 40%, exercise-induced arrhythmias or pathogenic variants in LMNA or TMEM43.</i> | III | C |
| Primary prevention of SCD: | | |
| ICD implantation should be considered in patients with DCM/NDLVC, with: <i>- symptomatic heart failure (NYHA class II–III), and LVEF \leq 35% after \geq 3 months of OMT.</i> | Ila | A |
| | Ila | C |

| | | |
|---|-----|---|
| <ul style="list-style-type: none"> - LVEF < 50% and ≥ 2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20 genes). - a pathogenic mutation in LMNA gene, if the estimated 5-year risk of life-threatening VA is $\geq 10\%$ ⁽¹⁾ and in the presence of NSVT or LVEF < 50% or AV conduction delay. | Ila | B |
| In DCM/NDLVC patients, electrophysiological evaluation should be considered when syncope remains unexplained after non-invasive evaluation. | Ila | C |
| Secondary prevention of SCD and treatment of VAs: | | |
| In patients with DCM/NDLVC, ICD implantation: | | |
| <ul style="list-style-type: none"> - is recommended in patients who survive SCA due to VT/VF or experience haemodynamically not-tolerated SMVT. - should be considered in patients with haemodynamically tolerated SMVT. | I | B |
| | Ila | C |
| Catheter ablation in specialized centres should be considered in patients with DCM/NDLVC and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated. | Ila | C |
| The addition of oral amiodarone or replacement of beta-blockers by sotalol should be considered in patients with DCM/NDLVC and an ICD who experience recurrent, symptomatic VA despite optimal device programming and beta-blocker treatment. | Ila | B |
| Management of relatives of a patient or SCD victim with DCM/HNDCM: | | |
| In a first-degree relative of a DCM/NDLVC patient, an ECG and an echocardiogram are recommended if: | | |
| <ul style="list-style-type: none"> - the index patient was diagnosed < 50 years of age or has clinical features suggestive of an inherited cause, or - there is family history of DCM/NDLVC, or premature unexpected SD. | I | C |
| In a first-degree relative of a patient with apparently sporadic DCM/NDLVC, an ECG and an echocardiogram may be considered. | IIb | C |

(1) Based on the risk calculator <https://lmna-risk-vta.fr/>

Prognosis:

- **The worst prognosis is seen with the following three cardiomyopathies: (HAD)**
HIV cardiomyopathy, amyloidosis, and doxorubicin-associated cardiomyopathy.
- **Some DCMs may be reversible ⁽¹⁾:**
 - **Abnormal energetic:** Tachycardia-induced cardiomyopathy, Cardiomyopathy related to thyroid disorders.
 - DCM associated with **inflammatory/immune** response: Myocarditis, Peripartum cardiomyopathy.
 - **Toxin-induced cardiomyopathy:** Alcoholic cardiomyopathy reverses if the alcohol is stopped at an early stage ± thiamine supplemented.
 - **Stress-related cardiomyopathies:** Takotsubo cardiomyopathy, other sepsis or critical illness-associated cardiomyopathy, and neurogenic cardiomyopathy (following hemorrhagic or ischemic stroke).
- Besides GDMT, several additional predictors of reverse LV remodelling have been identified:
 - Female sex, a non-ischaemic HF aetiology and the absence of digoxin use (IMPROVE-HF study).
 - Higher baseline LVEF.
 - Lower LV end-diastolic diameter.
 - Lower extent of LGE on CMR (indicative of lower interstitial replacement fibrosis).
 - TTN mutation (Higher rate of LV reverse remodeling in up to 70%).
- **Poor prognostic factors:**
 - Clinical: Male sex, advanced age (> 60 years), Black race, NYHA class (III-IV).
 - ECG: Presence of LBBB.
 - Biomarkers: Higher natriuretic peptide levels.
 - Imaging: Lower baseline LVEF, significant mitral regurgitation, and more pronounced mid-wall myocardial LGE on CMR.

(1) Those patients possibly may be protected against SCD during the recovery phase with wearable defibrillators, thus avoiding the requirement for permanent ICD implantation.

N.B:

Immunosuppression (Azathioprine and Prednisone for 6-12 months) could be effective in achieving LV reverse remodelling and improvement in HF symptoms in patients with:

- Biopsy-proven, Virus-negative post-myocarditis DCM.
- Acute giant-cell and eosinophilic myocarditis
- Cardiac sarcoidosis.

Arrhythmia-mediated cardiomyopathy

Definition:

- Atrial and/or ventricular dysfunction occurs secondary to rapid (e.g., SVT) and/or asynchronous (e.g., PVC or RV pacing) myocardial contraction, partially or completely reversed after treatment of the cause.
- Two categories of the condition exist: the arrhythmia is the only reason for ventricular dysfunction (arrhythmia-induced), and another where the arrhythmia exacerbates ventricular dysfunction in a patient with concomitant heart disease (arrhythmia-exacerbated).

Pathophysiology:

The mechanisms are not fully defined, but include depletion of energy stores and oxidative stress. In a way, it is a form of ischemic hibernation.

It has been suggested that chronic tachycardia that occurs > 10-15% of the day may result in cardiomyopathy. There is no precise ventricular rate known to lead to TCMP, although rates > 100 bpm are generally thought to be deleterious. However, in the case of PVCs or RV pacing, it is not only a high heart rate, but also asynchronous myocardial contraction, that can lead to LV dysfunction. PVCs burden of > 10% of the patient's total rhythm on a Holter monitor, may also lead to this cardiomyopathy.

Diagnosis:

- The classic clinical presentation is with symptoms and signs of congestive HF. It should be noted that patients may not necessarily present with an arrhythmia, therefore a high index of suspicion needs to be maintained.
- Patients may be diagnosed through echocardiography before the onset of clinical symptoms or after developing progressive HF.
- The following parameters suggest Arrhythmia-induced (vs Arrhythmia-aggravated) cardiomyopathy:
 - Shorter intrinsic QRS duration.

- Smaller LV end-diastolic diameter.
- Absence of LGE on CMR (Presence of LGE suggests underlying structural heart disease).
- LVEF improvement/normalization (reverse remodelling) following suppression of the arrhythmia.

Treatment:

After HF is treated (diuresis) and compensated, the tachyarrhythmia is targeted with a heart rate goal < 80 bpm. In addition, rhythm control is often attempted (e.g., ablation for atrial flutter and atrial tachycardia, DC cardioversion and antiarrhythmics for AF).

Prognosis:

This cardiomyopathy usually reverses several months after rate control, typically within 6 months. Residual ultrastructural abnormalities persist, explaining a fast recurrence of LV dysfunction with recurrence of the arrhythmia.

Table 4-13: ESC Recommendations for the therapy of SVT in patients with suspected or established heart failure due to tachycardiomyopathy:

| Recommendation | Class | Level |
|---|--------------|--------------|
| <i>It is recommended that tachycardia-induced cardiomyopathy (TCM) is considered in a patient with reduced LVEF with an elevated heart rate (> 100 b.p.m.).</i> | I | B |
| <i>24 h (or multiday) ambulatory ECG monitoring should be considered for diagnosis of TCM by identifying subclinical or intermittent arrhythmias.</i> | IIa | B |
| <i>Catheter ablation is recommended for TCM due to SVT.</i> | I | B |
| <i>Beta-blockers (from the list with proved mortality and morbidity benefits in HFrEF) are recommended for TCM due to SVT, when catheter ablation fails or is not applicable.</i> | I | A |

AV nodal ablation with subsequent pacing ('ablate and pace'), either biventricular or His bundle pacing, is recommended if the tachycardia responsible for the TCM cannot be ablated or controlled by drugs.

I

C

HIV cardiomyopathy

Pathophysiology:

HIV cardiomyopathy is often related to a direct myocardial HIV infection, but is sometimes related to an autoimmune process triggered by HIV, coinfections (e.g., CMV, Toxoplasma, EBV), or selenium deficiency.

It should be distinguished from a reversible, acute illness cardiomyopathy sometimes seen in hospitalized HIV patients.

Diagnosis:

HIV cardiomyopathy is typically seen in patients with CD4 counts < 400.

Patients with a progressive course should undergo an endomyocardial biopsy to rule out and treat opportunistic coinfections.

Treatment:

The effect of highly active antiretroviral therapy on stabilizing HIV cardiomyopathy is unclear.

Non-dilated left ventricular cardiomyopathy (NDLVC)

Diagnosis:

- **In index case:** NDLVC phenotype is defined by the presence of non-ischaemic LV scarring or fatty replacement regardless of the presence of global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring (as assessed by the presence of LGE on CMR) that is unexplained solely by abnormal loading conditions (hypertension, valve disease) or CAD.
- **In relatives:**
 - Clinical testing in relatives may reveal non-diagnostic abnormalities. In this context, NDLVC in a first-degree relative of an individual with NDLVC is suggested by: the presence of LV systolic global or regional dysfunction, or additional ECG abnormalities (e.g. repolarization abnormalities, low QRS voltages, frequent PVCs [> 500 per 24 h] or NSVT).
 - In the absence of conclusive genetic information in the family, NDLVC should be considered familial if: **(i)** one or more first- or second- degree relatives have NDLVC, or **(ii)** when SCD has occurred in a first- degree relative at any age with an established diagnosis of NDLVC, or **(iii)** if a first-degree relative has sudden death at < 50 years of age and autopsy findings suggestive of the NDLVC phenotype.

Diagnostic workup: As discussed before, but with special considerations to the following:

- **ECG features:** Resting and ambulatory ECG testing are of particular importance in patients with NDLVC, as **(I)** conduction disease, and atrial and ventricular arrhythmia may often be early phenotypic features, **(II)** specific features can indicate the underlying genetic cause:
 - Prolonged PR or AV block is frequent in neuromuscular causes of NDLVC and in sarcoidosis.
 - Laminopathies are characterized by prolonged PR interval, AF, and ventricular ectopics, and frequently show low voltage in pre-cordial leads.
 - NDLVC caused by DSP and PLN variants frequently show depolarization abnormalities such as low QRS voltage.

- **Cardiac MRI:** Cardiac MRI with LGE is the foremost imaging modality in NDLVC as it provides confirmation of the presence of non-ischaemic myocardial fibrosis that is essential for the diagnosis in most cases. It can also provide clues to the underlying aetiology (e.g. subepicardial distribution in post-myocarditis forms, patchy in sarcoidosis, extensive inferolateral in dystrophinopathies, septal mid-wall in LMNA carriers, and ring-like in DSP and FLNC variant carriers).

Table 4-14: ESC Recommendations for resting and ambulatory ECG monitoring in patients with NDLVC:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Ambulatory ECG monitoring is recommended in patients with NDLVC annually or when there is a change in clinical status, to aid in management and risk stratification.</i> | I | C |

Genetic testing:

- Genetic testing is recommended in all patients with NDLVC, as the identification of a P/LP gene variant in a patient with NDLVC allows better prediction of the disease outcome and progression, may contribute to the indications for device implantation, and allows familial screening for relatives.
- The genes most commonly implicated in NDLVC are DSP, FLNC (truncating variants), DES, LMNA, or PLN. Desmoplakin (DSP) variants, in particular, cause a unique form of cardiomyopathy with a high prevalence of LV fibrosis and myocardial inflammatory episodes.

SCD prevention:

The same as discussed before in DCM

Traits and syndromes associated with cardiomyopathy

Left Ventricular Non-compaction (LVNC)

- The term 'LVNC' has been used to describe a ventricular phenotype characterized by prominent LV trabeculae and deep intertrabecular recesses. The myocardial wall is often thickened with a thin, compacted epicardial layer and a thicker endocardial layer ⁽¹⁾.
- Recently, LVNC is not considered to be a cardiomyopathy in the general sense. Instead, it is seen as a phenotypic trait that can occur either in isolation or in association with other developmental abnormalities, ventricular hypertrophy, dilatation, and/or systolic dysfunction. LVNC is frequently a familial trait and is associated with variants in a range of genes, including those encoding proteins of the sarcomere, Z-disc, cytoskeleton, and nuclear envelope.
- LVNC has also been used to describe an acquired and sometimes transient phenomenon of excessive LV trabeculation (e.g. in athletes, during pregnancy, or following vigorous activity) that must reflect increased prominence of an otherwise normal myocardial architecture.
- Given the lack of morphometric evidence for ventricular compaction in humans, the term '**hypertrabeculation**', rather than LVNC, is recommended, particularly when the phenomenon is transient or clearly of adult onset.

Diagnosis:

- LV non-compaction has been defined as an end-systolic ratio of the loose inner myocardium to the compacted outer myocardium ≥ 2 , with an impaired or normal LVEF.
- Doppler flow is seen through the recesses and helps define the excessively trabeculated morphology.
- Occasionally, LV non-compaction may be mistaken for LV thrombus, but echo contrast allows the differentiation. In fact, the deep sluggish recesses allow for thrombus formation.

Anticoagulation is generally indicated when EF < 40% or there is LV thrombus, systemic embolism, or AF.

(1) Embryologically, the normal myocardium has subendocardial and subepicardial layers that are initially loose then become packed and thin, i.e., compacted. Historically, it was thought that in LVNC or "spongy myocardium," the subepicardium becomes compacted but the subendocardial meshwork remains loose, leading to prominent trabeculations and deep recesses, particularly in the mid-LV and apex.

Prognosis:

The prognosis depends on the underlying LVEF and HF functional status.

Takotsubo Syndrome

Stress-induced cardiomyopathy or Transient apical ballooning syndrome

Takotsubo syndrome is characterized, in its most typical variant, by transient regional systolic dysfunction, dilatation, and oedema involving the LV apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography. Takotsubo syndrome (TTS) can mimic MI and is found in 1–2% of patients presenting with suspected STEMI.

Pathophysiology:

- This is a transient form of cardiomyopathy that occurs after emotional or physical stress and typically leads to dyskinesis and “ballooning” of the ventricular apex (Takotsubo stunning).
- Takotsubo stunning results from: excessive release of cardiac neuronal and systemic catecholamines, impaired microvascular perfusion, myocardial inflammation, and electrophysiological derangements.
- Atypical variants of Takotsubo syndrome have been described, such as the mid-ventricular ballooning and the basal ballooning (inverted Takotsubo syndrome).
- Takotsubo syndrome typically involves post-menopausal women (~95% of cases), and only 2% of cases are < 50 years.

Diagnosis:

- Takotsubo syndrome uncommonly presents as HF and more typically mimics STEMI, and presents with chest pain, anterior ST elevation (with rare inferior extension) with deep anterior T-wave inversion, and elevated troponin (the peak cTn values observed are modest, and contrast with the large territory of ECG changes or LV dysfunction).
ST elevation evolves into deep anterior T-wave inversion and prolonged QT within 24-48 hrs; patients sometimes present at the stage of T-wave inversion without residual ST elevation. Transient anterior/lateral Q waves are seen in 30% of the cases.

- On TTE and left ventriculography, the apex is akinetic/dyskinetic while the base is hypercontractile, and the overall EF is 20-40%. RV is commonly involved (~1/3 of cases). Up to 17% of TCs are mid-cavitary rather than apical. Functional MR is seen in ~20% of Takotsubo syndrome cases (due to LV dilatation or LVOT obstruction/SAM).
- Coronary angiography should be performed in all these cases to rule out LAD disease. In TC, no significant CAD is found.
- As opposed to STEMI and myocarditis, MRI does not show any LGE (while helpful, MRI is not a necessary diagnostic tool).

Treatment:

HF and cardiogenic shock may result from the poor LV function but also from the basal hypercontractility that leads to LVOT obstruction, the latter being seen in ~15% of Takotsubo syndrome cases. These two forms of HF or shock need to be differentiated by TTE and are treated differently.

- In LVOT obstruction: inotropes are avoided; β -blockers are used if HF is present (carefully), while IV fluids and α -agonists are used if shock is present.
- In cardiogenic shock due to poor LV function: Catecholamine administration should be avoided, as already have a causative relationship with the syndrome. Milrinone also should be avoided (appears to trigger Takotsubo syndrome in pre-clinical models via increasing cardiomyocyte cAMP levels). Levosimendan, which does not increase cAMP, seems a rational approach.

Prognosis:

- All cases of Takotsubo syndrome are reversible within 2 months (half of them resolve within a week).
- Takotsubo syndrome has a good prognosis, with ~1% in-hospital mortality.
- Complications may be seen acutely, but are much less common than in STEMI: HF (17%), shock (4%), VT/VF (1-6%), LV thrombus (2.5%) with a stroke risk of ~1%, usually within 48 hours.

Other stress-related transient cardiomyopathies:

- **Neurogenic stress cardiomyopathy** is seen in up to 20-30% of patients with subarachnoid hemorrhage, and less often in ischemic stroke. As opposed to Takotsubo syndrome, it usually involves the basal and mid-ventricular segments and spares the apex.

- **Septic or acute medical illness cardiomyopathy:** ~50% of septic patients develop a septic cardiomyopathy. It results from the myocardial depressant effect of cytokines (TNF- α) and is usually characterized by diffuse global hypokinesis. The RV is involved as well. Septic cardiomyopathy always normalizes within 7-10 days.

Arrhythmogenic Right Ventricular Cardiomyopathy ⁽¹⁾

(Also known, Arrhythmogenic cardiomyopathy)

Definition:

Inherited heart muscle disease characterized by progressive fibrofatty replacement of the ventricular myocardium which may act as a substrate for VAs, unexplained syncope and/or sudden cardiac death.

ARVC presents between 10-50 years of age, more commonly in *men*, and is familial in 30% of the cases (*autosomal dominant*). It is caused by pathogenic mutations in *desmosomal* genes.

Pathology:

In arrhythmogenic cardiomyopathy, myocardial atrophy is a genetically determined process that occurs progressively with time, starts from the epicardium and extends toward the endocardium to become transmural, resulting into progressive wall thinning. As a consequence, the pathognomonic gross features of AC consist of single or multiple aneurysms, predominantly located in the RV. However, LV involvement occurs in up to 76% of cases.

(1) Arrhythmogenic Right Ventricular dysplasia (ARVD) was first described in 1982 and was thought to be the result of a congenital defect of myocardial development, and this perspective contributed to the early designation of 'dysplasia' (ARVD). As genetic and phenotypic characterization of the disease evolved, the term dysplasia was replaced by 'cardiomyopathy' (ARVC). Although the original disease phenotype was characterized by predominant RV involvement with minor and late LV disease, clinical variants characterized by early and greater LV involvement, which may parallel (i.e, biventricular AC) or exceed (i.e, left-dominant AC) the severity of RV involvement, have been increasingly reported. These findings have led to use the broader term of "arrhythmogenic cardiomyopathy".

N.B: The condition should not be confounded with **Uhl disease**, a congenital heart defect in which the RV myocardium fails to develop during embryonic life with the epicardium applied directly to endocardium in the absence of intervening fat.

Diagnosis:

- **Index case:** In 1994, a scoring system for clinical diagnosis of ARVC was proposed by an International Task Force. In 2010, Revised Task Force criteria was proposed to improve specificity of the diagnosis ⁽¹⁾. The diagnosis of ARVC was fulfilled in the presence of 2 major criteria, 1 major plus 2 minor, or 4 minor criteria from different categories. **The major criteria are:**
 - **ECG:**
 - Epsilon wave (reproducible low-amplitude signals between end of QRS complex to the onset of T wave) in the right precordial leads (V₁ to V₃).
 - VT of LBBB morphology with superior axis.
 - **Echo criteria:** RVOT on the long- or short-axis views (≥ 32 mm or 36 mm, respectively) **or** FAC $< 35\%$.
 - **MRI features:** regional RV akinesia or dyskinesia or dyssynchronous RV contraction **and** one of the following: RVEF $< 40\%$ **or** RVEDVi > 110 ml/m² (male) or > 100 ml/m² (female).
 - **RV angiography:** Regional RV akinesia, dyskinesia or aneurysm.
 - **Endomyocardial biopsy** showing fibrous replacement of the RV free wall myocardium with or without fatty replacement and with residual myocyte $< 60\%$ by morphological analysis.
 - **Family history:**
 - ARVC confirmed clinically or pathologically at autopsy in first degree relative.
 - Identification of pathogenic gene mutation associated with ARVC.

N.B:

(1) In 2020, the Padua criteria have offered an updated iteration to include LV involvement, but are yet to be externally validated.

- T-wave inversion seen in leads V₁-V₃, and in the absence of complete RBBB, is highly suggestive of ARVD. Normal women may have T-wave inversion in V₁-V₂ that rarely (4%) extends to V₃.
- ECG typically shows prolongation of QRS ≥ 110 ms that is localized to leads V₁-V₃, and more importantly, delayed S upstroke (nadir of S to end of QRS ≥ 55 ms in 95% of patients). QRS is normal in lead V₆.
- RBBB, whether complete or incomplete, is uncommon but may be seen in advanced stages.
- ECG abnormalities become more prevalent with time.
- Late potentials on signal-averaged ECG are also sensitive for ARVD diagnosis (minor criteria).

Table 4-15: ESC Recommendations for resting and ambulatory ECG monitoring in patients with ARVC:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Annual ambulatory ECG monitoring is recommended in patients with ARVC to aid in diagnosis, management, and risk stratification.</i> | I | C |

- **In relatives:** Clinical testing in relatives often reveals non-diagnostic abnormalities. In this context, ARVC in a first-degree relative of an individual with ARVC is suggested by: **(i)** Presence of RV systolic global or regional dysfunction, or **(ii)** additional ECG abnormalities (e.g. repolarization abnormalities, prolonged terminal activation duration, low QRS voltages, frequent PVCs [> 500 per 24 h], or NSVT).

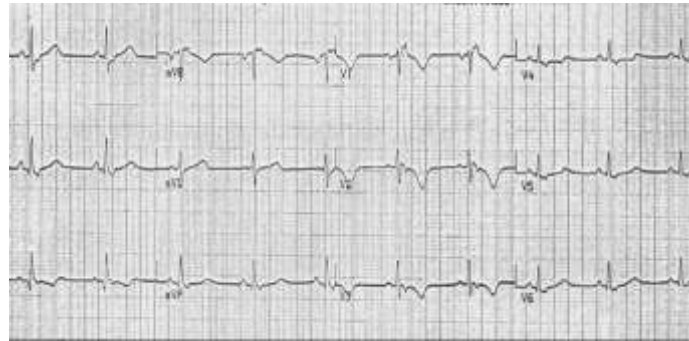


Figure 4-7: Arrhythmogenic Right Ventricular Cardiomyopathy. This 12-lead ECG tracing shows sinus rhythm with T-wave inversion over the right precordial leads. There is an epsilon wave (small deflection at the end of the QRS complex), in lead V₁.

Genetic testing

- Pathogenic or likely pathogenic variants can be identified in up to 60% of patients with ARVC.
- The genes underlying ARVC mainly encode proteins of the cardiac desmosome: plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin (JUP). The pattern of inheritance in the majority of ARVC families is autosomal dominant.
- **Indication:**
 - Must be offered to all patients with a suspected AC.
 - Must be offered to all first-degree adult relatives of patients with AC and a definite disease-causing mutation, regardless of their phenotype.
- Cardiac evaluation should be adapted to the particular risk of complications in the family. Evaluation every 1–2 years including ECG, ECHO, and Holter/ECG monitoring is generally recommended for relatives at risk of developing the disease. Cardiac MRI should be considered at the baseline evaluation.

N.B: Mutations in desmoplakin cause **Carvajal syndrome** (keratoderma, woolly hair, and AC with LV predominance). Mutations in plakoglobin cause **Naxos disease** (palmoplantar keratoderma, woolly hair, and AC). Both are recessive inherited.

Differential Diagnosis (ARVC phenocopies):

- Sarcoidosis, myocarditis, RV infarction, DCM, Chagas disease, pulmonary hypertension, and CHD with volume overload (such as Ebstein anomaly, ASD, and partial anomalous venous return, left-to-right shunt, and pericardial agenesis).
- Idiopathic RVOT VT, which is usually benign. The idiopathic nature of VT is supported by the absence of family history, a normal basal 12-lead ECG, a normal ventricular structure by cardiac imaging and electroanatomic mapping, a single VT morphology, and the non-inducibility at PES.
- Athlete's heart: In highly trained competitive athletes, RV enlargement, ECG abnormalities, and arrhythmias reflect the increased haemodynamic load during exercise. While global RV systolic dysfunction and/or RWMAs, such as aneurysms, are more in keeping with ARVC, the absence of overt RV structural changes, frequent PVCs, or inverted T in pre-cordial leads all support a benign nature.

Treatment:

- Affected individuals and desmosome gene mutation carriers avoid competitive or endurance sport activity in order to slow the pace of disease progression and reduce the ventricular arrhythmia burden.
- HF treatment (ACEIs, diuretics) is used in patients who develop RV or biventricular dysfunction.
- Beta-blockers is first-line therapy regardless of symptoms and arrhythmic manifestations because of its ability to lower the risk of exercise-induced VAs and to hinder myocardial disease progression by lowering the ventricular workload.
- AAD therapy (amiodarone and flecainide) should be considered in case of recurrent symptomatic VT.
- ICD implantation is indicated if:
 - Arrhythmic syncope in patients with definitive ARVC.
 - RV and LV dysfunction (RV FAC \leq 17% or RV EF \leq 35%, LVEF \leq 35%).

- Symptomatic ARVC patients with moderate RV (< 40%) and/or LV dysfunction (< 45%) and who have either NSVT **or** have SMVT inducible at PES.
- Catheter ablation is reserved for patients with recurrent, symptomatic SMVT or ICD shocks for SMVT despite beta-blockers. Since the ARVD process starts at the epicardial level, VT ablation is only effective if ablation is performed at combined approach (both endocardial and epicardial).

| Table 4-16: ESC Recommendations for management of patients with ARVC: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Diagnostic evaluation and general recommendations: | | |
| <i>In patients with suspected ARVC, CMR is recommended.</i> | I | B |
| <i>In patients with a suspected or definite diagnosis of ARVC, genetic counselling and testing are recommended.</i> | I | B |
| <i>Avoidance of high-intensity exercise is recommended in patients with a definite diagnosis of ARVC.</i> | I | B |
| <i>Avoidance of high-intensity exercise, including competitive sport, may be considered in genotype-positive/phenotype-negative individuals in families with ARVC.</i> | IIb | C |
| Primary prevention of SCD: | | |
| <i>ICD implantation should be considered in patients with definite ARVC and</i> <ul style="list-style-type: none"> - arrhythmic syncope. - severe RV or LV systolic dysfunction - symptomatic patients (presyncope or palpitations suggestive of VA) with moderate RV or LV dysfunction, and either NSVT or inducibility of SMVT at PES | IIa | B |
| | IIa | C |
| | IIa | C |
| <i>The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.</i> | IIa | B |

| | | |
|---|------------|----------|
| <i>In patients with ARVC and symptoms highly suspicious for VA, PES may be considered for risk stratification.</i> | IIb | C |
| Secondary prevention of SCD and treatment of VAs: | | |
| <i>In ARVC, ICD implantation</i> | | |
| <i>- is recommended in patients who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.</i> | I | A |
| <i>- should be considered in ARVC patients with haemodynamically tolerated SMVT.</i> | IIa | C |
| Antiarrhythmic management of ARVC: | | |
| <i>Beta-blocker is recommended in ARVC patients with ventricular ectopics, NSVT, and VT.</i> | I | C |
| <i>Beta-blocker therapy may be considered in all patients with a definite diagnosis of ARVC.</i> | IIb | C |
| <i>Amiodarone should be considered when regular beta-blocker therapy fails to control arrhythmia-related symptoms in patients with ARVC.</i> | IIa | C |
| <i>Flecainide in addition to beta-blockers should be considered when single agent treatment has failed to control arrhythmia-related symptoms in patients with ARVC.</i> | IIa | C |
| <i>Catheter ablation with availability for epicardial approach guided by 3D electroanatomical mapping of VT should be considered in patients with ARVC and recurrent, symptomatic SMVT or ICD shocks for SMVT despite beta-blockers.</i> | IIa | C |
| <i>In ARVC patients with indication for ICDs, a device with the capability of ATP programming for SMVT up to high rates should be considered.</i> | IIa | B |
| Management of relatives of a patient with ARVC: | | |
| <i>In a first-degree relative of a patient with ARVC, ECG and echocardiogram are recommended.</i> | I | C |

Prognosis:

Sudden death is common in ARVD; in fact, 25% of patients die suddenly.

When arrhythmic death is prevented, patients live long enough to develop severe RV then LV failure.

Restrictive Cardiomyopathy (RCM)

Definition:

RCM is defined as restrictive left and/or RV pathophysiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness. It is associated with the worst prognosis of all the cardiomyopathy phenotypes.

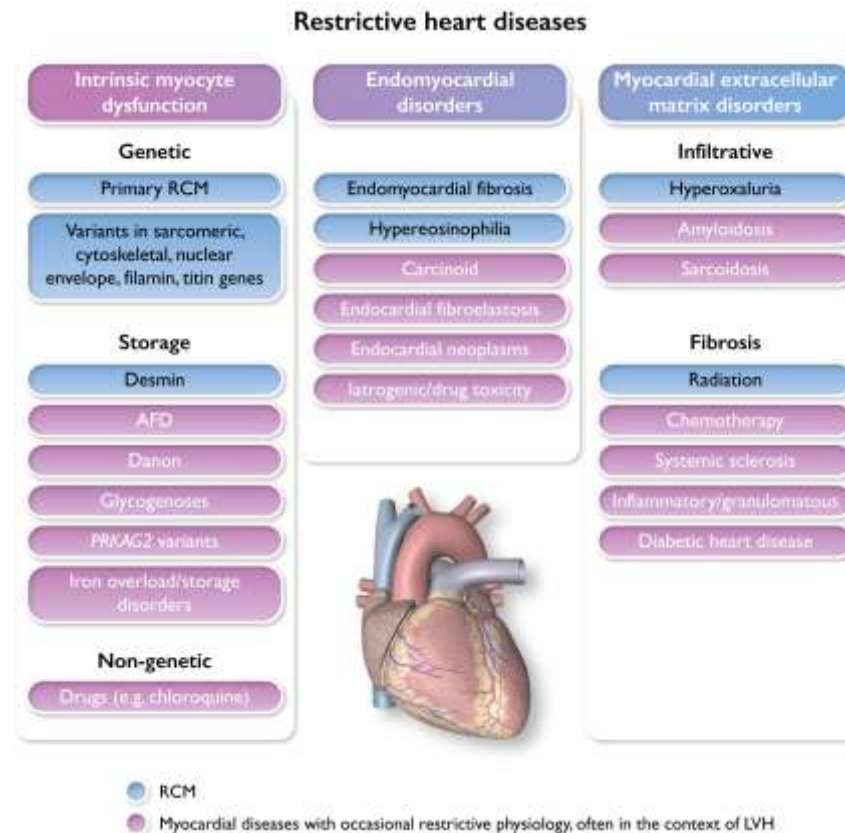


Figure 4-8: Spectrum of restrictive heart diseases. AFD, Anderson–Fabry disease; PRKAG2, Protein kinase AMP-activated non-catalytic subunit gamma 2. In **primary RCM**, abnormal ventricular stiffness has been attributed to increased myofilament sensitivity to calcium, increased deposition of collagen type III, and intracellular aggregates of the mutant protein such as desmin or filamin C. In **infiltrative and storage diseases**, extracellular or intracellular accumulation of the pathological material in the myocardium accompanied by cardiomyocyte hypertrophy and interstitial and/or replacement fibrosis are responsible for increased myocardial stiffness. **Source:** 2023 ESC Guidelines for the management of cardiomyopathies.

N.B:

The clinical phenotype of cardiomyopathy due to specific aetiologies may overlap between HCM and RCM (e.g., in Anderson-Fabry, Pompe and Danon diseases), or a transformation from an RCM to DCM due to progressive nature of the underlying disorder (e.g., haemochromatosis, sarcoidosis, amyloidosis).

Features of RCM:

• Morphological Features:

- LV is small and stiff with severe diastolic failure caused by abnormalities intrinsic to the myocardium, or to the endomyocardial layer.
- Systolic function is preserved (at least when assessed using LVEF), but tends to deteriorate over time (with an evolution towards a hypokinetic-dilated phase).
- LA and RA are markedly dilated and functional TR and MR, sometimes severe.
- The myocardial thickness is normal or near-normal in idiopathic restrictive cardiomyopathy, but is increased in infiltrative cardiomyopathies, particularly amyloidosis, and may occasionally be asymmetric.

N.B:

- RCM is characterized by high risk of thromboembolism, conduction abnormalities, arrhythmias and SCD.
- Restrictive physiology can occur in patients with end-stage hypertrophic and dilated cardiomyopathy; the preferred terms are 'hypertrophic' or 'dilated cardiomyopathy with restrictive physiology'.

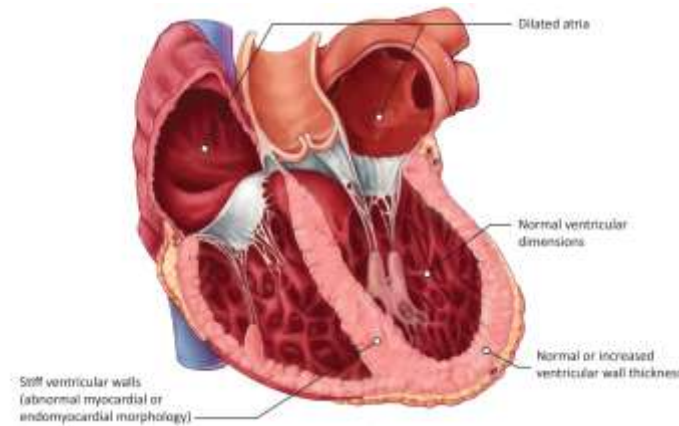


Figure 4-9: Characteristic alterations in cardiac morphology underlying heart failure in restrictive cardiomyopathy.

Source: Seferović, P.M., Polovina, M., et al. (2019), Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*, 21: 553-576

- **Imaging features:**

- The first clue of restrictive pathophysiology is the combination of biatrial enlargement (not due to specific causes such as valve disease or AF), normal or mildly impaired and non-dilated ventricles.
- Doppler imaging can then show a restrictive filling pattern of transmitral flow with increased E wave (due to elevated LA pressure), and decreased A wave (due to the high ventricular diastolic pressure), reduction of mitral deceleration time, and isovolumetric relaxation time. Additionally, the ratio between systolic and diastolic pulmonary venous flow ratios is reduced (because of high LA pressure).
- Tissue Doppler shows reduced early diastolic myocardial velocity (e') leading to an elevated E/e' .
- Congestion of the IVC and diastolic flow reversal in the hepatic veins during inspiration are common (inability of a non-compliant RV to accommodate the increased venous return).

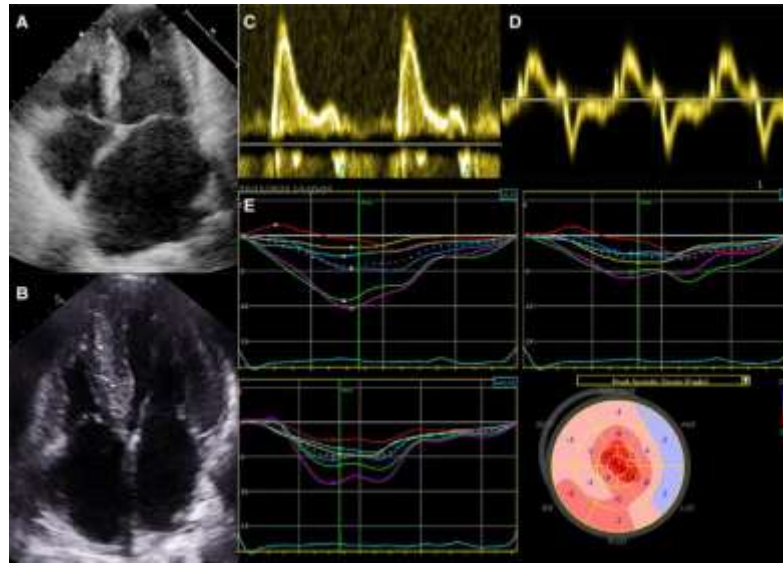


Figure 4-10: Echocardiography in restrictive cardiomyopathies. (A) Small LV cavity size in presence of significantly increased wall thickness and severe LA dilatation; (B) biventricular wall thickening in absence of pulmonary hypertension; (C and D) restrictive filling pattern with elevated E/E' ratio in keeping with increased LV filling pressures; (E) myocardial strain analysis showing an apical sparing pattern in a patient with cardiac amyloidosis. **Source:** Rapezzi C, Aimo A, Barison A, et al. Restrictive cardiomyopathy: definition and diagnosis. *European Heart Journal*. 2022 Dec 1;43(45):4679-93.

- **Hemodynamic features:**

RCM is characterized by elevated diastolic filling pressures and a rapid equalization of filling pressures of the four cardiac chambers during diastole, with a frequent 'dip and plateau' or 'square root' pattern on pressure tracings. This pattern becomes more evident with manoeuvres that augment ventricular filling, such as volume infusion or leg raising.

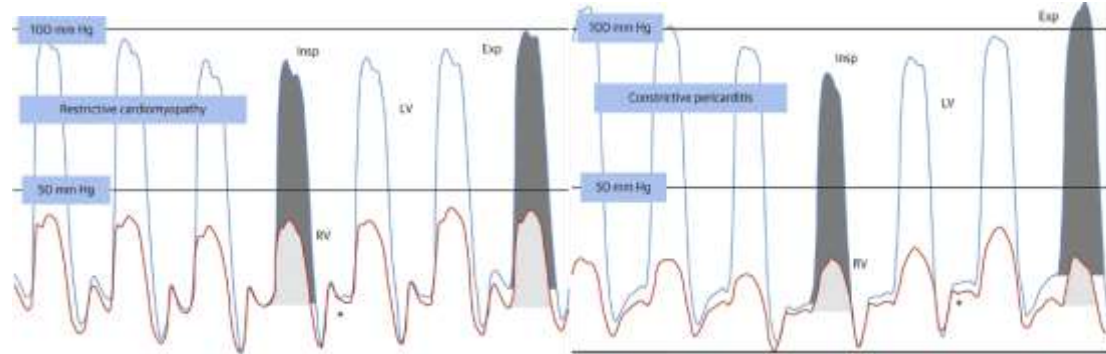


Figure 4-11: Simultaneous RV and LV haemodynamic assessment in constrictive pericarditis and restrictive cardiomyopathy. (Left) LV and RV pressure tracings in **restrictive cardiomyopathy**. End-diastolic pressures are elevated and a square root sign (*) is seen; there is no evidence of enhanced ventricular interdependence, with parallel changes in LV and RV pressure curve areas. **(Right)** LV and RV hemodynamic pressure tracings in **constrictive pericarditis**. End-diastolic filling pressures are elevated, and a 'square root' sign is present on both tracings (*). Enhanced ventricular interdependence is present, demonstrated by visualization of the systolic area index, RV (light grey) and LV (dark grey) areas under the curve for both inspiration (Insp) and expiration (Exp). During inspiration, there is an increase in the area of the RV pressure curve and a decrease in the area of the LV pressure curve. **Source:** Rapezzi C, Aimo A, Barison A, et al. Restrictive cardiomyopathy: definition and diagnosis. *European Heart Journal*. 2022 Dec 1;43(45):4679-9

In a patient with a thick myocardium and severely restrictive filling/HF, three diagnoses are considered:

1. Hypertensive cardiomyopathy. 2. Hypertrophic cardiomyopathy. 3. Infiltrative cardiomyopathy.

As opposed to hypertrophic or hypertensive cardiomyopathy,

- The increase in thickness is due to myocardial infiltration rather than myocardial hypertrophy, explaining the discrepancy between the low voltage on the ECG and the thick myocardium on echocardiography.
- The thickening frequently involves both ventricles, not just the LV.

ECG and MRI help with the differential diagnosis.

Genetic testing:

- When inherited, RCM most commonly presents as an autosomal dominant disorder.
- Genes associated with RCM encode sarcomeric structural and regulatory proteins and cytoskeletal intermediate filaments. Although all major sarcomeric genes may cause RCM, the most common disease gene is TNNI3, which encodes the thin filament troponin I.
- Restrictive cardiomyopathy can be associated with intramyocyte accumulation of unfolded defective proteins, a feature that is increasingly demonstrated in carriers of defects in DES, FLNC, and BAG3.

Management:

| Table 4-17: ESC Recommendations for management of patients with restrictive cardiomyopathy: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended that multimodality imaging be used to differentiate RCM from HCM or DCM with restrictive physiology.</i> | I | C |
| <i>It is recommended that baseline cardiac and non-cardiac investigations are performed to assess involvement of the neuromuscular system or other syndromic disorders.</i> | I | C |
| <i>Cardiac catheterization is recommended in all children with RCM to measure pulmonary artery pressures and PVR at diagnosis and at 6–12 monthly intervals to assess change in PVR.</i> | I | B |
| <i>ICD implantation is recommended to reduce the risk of sudden death and all-cause mortality in patients with RCM who have survived a cardiac arrest <u>or</u> have recovered from a ventricular arrhythmia causing haemodynamic instability.</i> | I | C |
| <i>Endomyocardial biopsy should be considered in patients with RCM to exclude specific diagnoses (including iron overload, storage disorders, mitochondrial cytopathies, amyloidosis, and granulomatous myocardial diseases) and to diagnose restrictive myofibrillar disease caused by desmin variants.</i> | IIa | C |

ICD implantation may be considered in children with RCM who have evidence of myocardial ischaemia and syncope.

IIb

C

Prognosis:

- Restrictive cardiomyopathy is associated with the worst prognosis of the cardiomyopathy phenotypes.
- The prognosis of RCM largely depends on the restrictive physiology, regardless of the underlying cause.
- In adult patients with genetic RCM, the main cause of death is heart failure (more than 40%), with a 5-year survival rate of ~50%.
- More than 50% of children with RCM are at risk of death or transplantation shortly after diagnosis. Up to 75% of surviving patients demonstrate heart failure. Elevated pulmonary vascular resistance (PVR) is present in up to 40% of children with RCM, which has an impact on suitability for and timing of cardiac transplantation. Cardiac catheterization with an assessment of PVR is therefore recommended in all children at diagnosis and every 6 to 12 months.

Amyloidosis

The systemic amyloidoses are a broad spectrum of diseases that result from **misfolding of proteins** that aggregate into **b-sheet amyloid fibrils**. Over 35 amyloidogenic precursor proteins have been identified that give rise to diseases characterized by extracellular deposition of insoluble amyloid fibrils in various organs.

In cardiac amyloidosis, amyloid fibrils accumulate in the interstitial space between cardiac myocytes, precipitating cellular injury and impairing compliance. Advanced cardiac amyloidosis is physiologically characterized as a restrictive cardiomyopathy.

The nomenclature for systemic amyloidosis includes an “A” for amyloid followed by an abbreviation of the protein that misfolds. The majority of amyloid cardiomyopathy will be caused by misfolding of 2 proteins:

- (1) Monoclonal immunoglobulin light chain produced in bone-marrow plasma cell disorders (AL amyloidosis); and
- (2) Transthyretin (TTR), also known as pre-albumin, a thyroxine and retinol (vitamin A) transport protein produced mainly by the liver (ATTR amyloidosis).

Misfolding and aggregation of TTR in ATTR-CM occurs in the context of genetically normal protein, known as senile/wild-type transthyretin amyloidosis (ATTRwt). Alternatively, ATTR caused by mutations rendering TTR prone to misfolding is termed variant/hereditary transthyretin amyloidosis (hTTR).

Definition:

Cardiac amyloidosis is characterized by the extracellular deposition of misfolded proteins in the ventricular myocardium with the pathognomonic histological property of green birefringence when viewed under cross-polarized light after staining with Congo Red.

Pathophysiology:

Although nine types of cardiac amyloidosis have been described, there are two main forms ⁽¹⁾:

1. Amyloid light-chain (AL) amyloidosis:

- It is usually seen at an age over 40-50.
- It results from direct toxicity of amyloidogenic light chains deposition by increased oxidative stress has been implicated in myocardial damage, which is often out of proportion to amyloid deposition. This may explain severe and progressive HF in patients with seemingly mild-to-moderate cardiac involvement.
- It may be primary or secondary to bone-marrow plasma cell disorders e.g., multiple myeloma.
- It is associated with amyloid renal failure and nephrotic syndrome.

2. Transthyretin (ATTR) amyloidosis:

- **Wild-type amyloidosis (ATTR-wt)**: occurs almost exclusively in elderly men (> 65 years) and is more slowly progressive than AL amyloidosis. It is the most frequent form of cardiac amyloidosis worldwide. It results from aberrant deposition of normal, wild-type transthyretin and usually only affects the myocardium. It is estimated that 6-16% of all patients with unexplained LVH or HFpEF or severe aortic stenosis undergoing aortic valve replacement, aged above 65 years, may have wtTTR-CA.
- **Hereditary transthyretin amyloidosis (hTTR)** (< 10% of cases) is related to the deposition of an abnormal transthyretin (autosomal dominant). It leads to cardiomyopathy and neuropathy (no renal involvement).

Diagnosis:

Cardiac amyloidosis should be suspected in patients with increased LV wall thickness in the presence of cardiac or extracardiac red flags, particularly in patients > 65 years of age.

(1) Other rare causes of cardiac amyloidosis include serum amyloid A amyloidosis (AA), hereditary apolipoprotein A-1, and apolipoprotein A-4 amyloidosis. AA amyloidosis may be suggested based on a history of chronic inflammatory disease (e.g., rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease).

Step (1): Red Flags (Clues suggesting a diagnosis of cardiac amyloidosis):

- **Clinical:** Hypotension or normotensive if previously hypertensive - Carpal tunnel syndrome - Polyneuropathy - Dysautonomia - Macroglossia and renal insufficiency (in AL-Amyloidosis).
- **ECG:** Pseudo-infarct ECG pattern - Low QRS voltage to degree of LV thickness ⁽¹⁾ - AV conduction disease.
- **Laboratory:** Disproportionally elevated NT-proBNP to degree of HF - Persisting elevated troponin levels.
- **Echocardiography:** Granular sparkling of myocardium - Increased thickness of the interatrial septum - Increased RV free wall thickness - Increased AV valves thickness - Pericardial effusion - Reduced longitudinal strain with apical sparing pattern (*cherry on top*).
- **Cardiac MRI** ⁽²⁾: Diffuse subendocardial LGE - Elevated native T1 values - Increased extracellular volume - Abnormal gadolinium kinetics.

Step (2): Monoclonal protein screen and Cardiac scintigraphy scan:

• **Monoclonal protein screen:**

- It is used to assess for the presence of plasma cell disorder, therefore, evidence for AL-amyloidosis.
- To exclude AL amyloidosis, monoclonal protein screen should include 3 tests: serum free light chain (sFLC), serum immunofixation electrophoresis (SIFE), and urine immunofixation electrophoresis (UIFE).

• **Cardiac scintigraphy with Tc-PYP followed by SPECT:**

- It is originally used in bone imaging, then emerged as a diagnostic imaging tool of TTR Amyloidosis.
- In scintigraphy, the radiotracers can persist in the ventricular cavity, producing an uptake signal that can be mistaken for myocardial uptake on planar imaging; hence, subsequent SPECT images must be acquired if uptake is present to distinguish myocardial uptake from the blood pool radiotracer signal.

(1) Low QRS voltage is only present in 30% of patients with cardiac amyloidosis. Thus, its absence does not exclude the diagnosis.

(2) It is important to note that CMR is neither necessary nor sufficient for establishing the diagnosis of cardiac amyloidosis as a standalone test and cannot distinguish between AL- Amyloidosis and ATTR-Amyloidosis.

Step (3): Endomyocardial biopsy:

- Before the advent of cardiac scintigraphy, the diagnosis of cardiac amyloidosis could only be made by histologic confirmation of amyloid deposits via EMB and Congo red staining.
- EMB should be performed in the following scenarios: **(A)** high clinical suspicion of cardiac amyloidosis in patient with monoclonal protein by SIFE and/or an abnormal sFLC; **(B)** high clinical suspicion for cardiac amyloidosis despite negative or equivocal Tc-PYP imaging; **(C)** cardiac scintigraphy is unavailable; or **(D)** to detect the subtype if both monoclonal protein screen and scintigraphy are diagnostic.

Step (4): Genetic testing in TTR Amyloidosis to establish the presence or absence of hereditary TTR. Distinguishing hTTR from TTRwt amyloidosis in the patient assists not only with cascade testing of at-risk relatives but also may inform treatment strategy, as mRNA silencers are currently only approved for use in the context of hTTR-associated neuropathy.

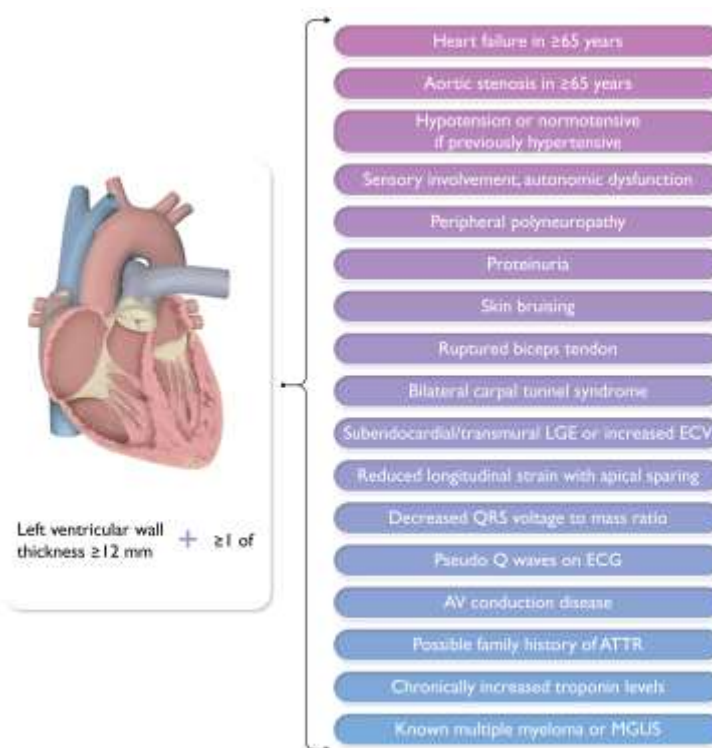


Figure 4-12: Screening for cardiac amyloidosis. Source: 2023 ESC Guidelines for the management of cardiomyopathies.

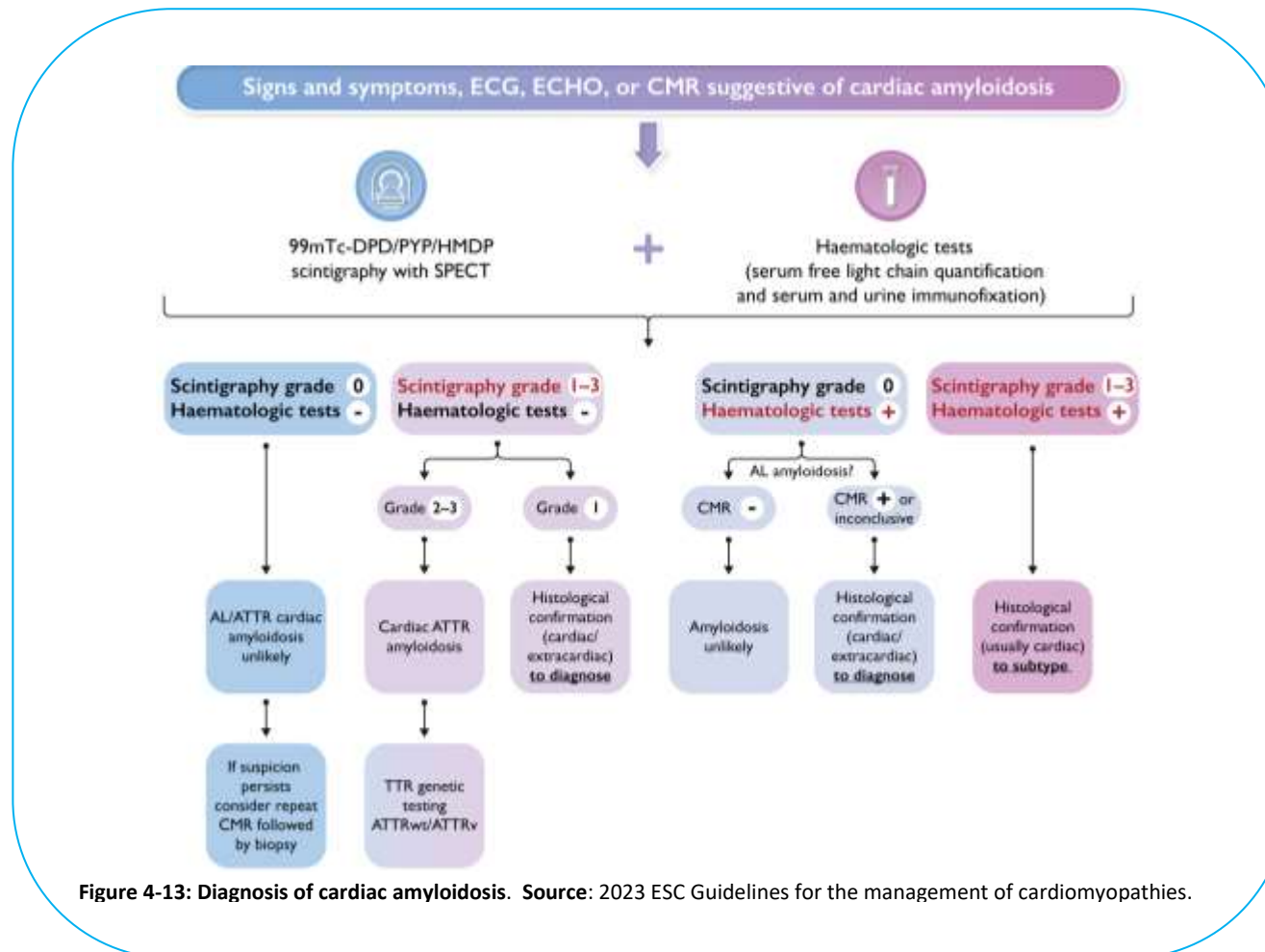


Figure 4-13: Diagnosis of cardiac amyloidosis. Source: 2023 ESC Guidelines for the management of cardiomyopathies.

Treatment:

- **Therapy of AL-CA** is based on treatment of the underlying haematological problem with chemotherapy or autologous stem-cell transplant.

- **Treatment of TTR-CA:**

- **Tafamidis** is the only medication approved by the FDA for treatment of ATTR cardiac amyloidosis. It acts as a TTR stabilizer, slowing the dissociation of TTR and thus fibril formation and cardiac deposition. It reduced all-cause mortality and CV hospitalizations in cardiac or non-cardiac biopsy-proven hereditary and wtTTR amyloidosis, mainly in those patients with NYHA class I and II at baseline. Functional improvement occurred within 6 months, whereas the decrease in mortality took nearly 2 years to occur.
- Hereditary TTR-Amyloidosis with polyneuropathy: IV **Patisiran** (small interfering RNA molecule) or Subcutaneous **Inotersen** (antisense oligonucleotide against TTR) may be considered.
- Liver and/or cardiac transplantation can be considered only in *end-stage disease of hTTR amyloidosis*.

- **Management of HF symptoms:**

- Maintenance of euvolaemia is central to management, but it is challenging due to the markedly reduced ventricular capacitance. Loop diuretics and MRAs should be used with caution since over-diuresis may lead to low output hypotension in the presence of restrictive filling abnormalities.
- The use of standard HF GDMT is poorly tolerated due to hypotension. Beta-blockers may cause an increased risk of worsening HF (because a fixed stroke volume requires a higher heart rate to maintain cardiac output). There is insufficient evidence regarding SGLT2-inhibitors efficacy.

- **Management of AF:**

- Amyloid infiltration of the atrial wall leads to atrial myopathy and electromechanical dissociation with high embolic risk. Patients with amyloidosis and history of AF should receive anticoagulation regardless of CHA₂DS₂-VASc score. There is no evidence to support anticoagulation for patients in SR, yet.
- Rate control: ventricular response rates in AF tend not to be elevated, although at times additional heart rate-lowering agents, such as low-dose beta-blockade, may be effective if tolerated without hypotension. Digoxin should be avoided as it has a high affinity for the amyloid and thus a high toxicity. CCB should also be avoided as they may cause severe hypotension, or form complexes with amyloid.

- Rhythm control can be considered if the patient remains symptomatic despite attempts at rate control, and amiodarone is generally well tolerated as a first-line agent. Catheter ablation in cardiac amyloidosis has suggested higher success rates in those with earlier-stage disease.

Table 4-18: ESC Recommendations for the treatment of transthyretin amyloidosis-cardiac amyloidosis:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|---------------------|---------------------|
| <i>Tafamidis is recommended in patients with wtTTR-CA and patients with genetic testing proven hTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.</i> | I | B |

Prognosis:

- **Patients with AL amyloidosis** have median survival \approx 6 months, and 5-year survival rate $< 10\%$. Increased levels of NT-proBNP and troponin T, and extracellular volume expansion on CMR T1 mapping have been shown to strongly predict poor survival in AL amyloidosis.
- **Patients with ATTR amyloidosis** (particularly those with ATTR-wt) have a longer median survival of 24-66 months compared with AL amyloidosis; nevertheless, the prognosis is poor.

Anderson-Fabry disease (AFD)

- **Definition:** AFD is an inborn error of metabolism where a deficient or absent enzyme, alpha-galactosidase A (α -Gal A), due to a pathogenic genetic variant in the GLA gene, causes the storage of some degradation cell products, mainly globotriaosylceramide (Gb3) in a patient's lysosomes.
 - It is X-linked inherited disease; males are therefore always affected, while females' organ involvement usually develops later in life but can become similar to males due to the lyonization phenomena ⁽¹⁾.
 - It is a multisystem disorder affecting particularly the heart, kidney, and brain.
- **Types:** Two Anderson–Fabry phenotypes can be distinguished:
 - Classic Anderson–Fabry: it is severe clinical phenotype characterized by absent or severely reduced ($< 1\%$ of mean normal) α -Gal A activity, marked Gb3 accumulation, and childhood or adolescent onset of symptoms followed by progressive multiorgan failure, is most often seen in males (but not exclusively) without residual enzyme activity.
 - A 'non-classical' Anderson–Fabry phenotype or later-onset phenotype with incomplete systemic involvement, which is seen in both males and females, with some level of residual enzyme activity, and in most cases manifesting as isolated cardiac involvement.
- **Diagnosis:**
 - Anderson–Fabry disease should be suspected in patients with LVH and additional cardiac and extracardiac red flags.
 - The diagnosis is established by assessment of α -GalA activity and lyso-Gb3 measurement in male patients; in females, genetic testing is usually required to confirm the diagnosis.
 - In children and adolescents, diagnosis is made by family history or based on other extracardiac symptoms, but overt LVH is usually not present.

Table 4-19: Anderson–Fabry disease red flags:

(1) Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than egg cells. This phenomenon is called X-inactivation or lyonization. X-inactivation ensures that females, like males, have one functional copy of the X chromosome in each body cell.

Extracardiac red flags:

- No male-to-male transmission in pedigree
- Renal involvement (dialysis, renal transplantation) or LVH in relatives
- Albuminuria
- Neuropathic pain
- Angiokeratomas
- Hypohidrosis, heat/cold and exercise intolerance
- Cornea verticillata
- Hearing loss (either progressive or sudden), tinnitus, vertigo
- GI symptoms (nausea, vomiting, non-specific abdominal pain, constipation, diarrhoea)

Cardiac red flags:**ECG**

- Short PQ interval in young patients
- Atrioventricular blocks in adult patients
- Bradycardia
- Chronotropic incompetence
- LVH

Echocardiogram

- LVH with normal systolic function
- Hypertrophy of papillary muscles
- Mitral and aortic valve thickening with mild-to-moderate regurgitation
- Reduced global longitudinal strain

CMR

- Basal-inferolateral late gadolinium enhancement

| | |
|-------------------|--|
| | <ul style="list-style-type: none"> ○ Low native T1 (caution with 'pseudonormalization' in areas affected by fibrosis) ○ High focal/global T2 |
| Laboratory | <ul style="list-style-type: none"> ○ Elevated high-sensitivity troponin ○ Elevated NT-proBNP |

- **Treatment:** Enzyme replacement therapy (**α -galactosidase infusions**) is indicated in all symptomatic patients with classical disease, including children, at the earliest signs of organ involvement. It is more effective when administered in the early stages of the disease, before irreversible tissue fibrosis takes place.
- **Prognosis:** 40% of patients die as a result of CV complications versus < 10% as a result of neurological or kidney complications. Potential risk factors for SCD: Higher age, male gender, NSVT, LVH, and LGE.

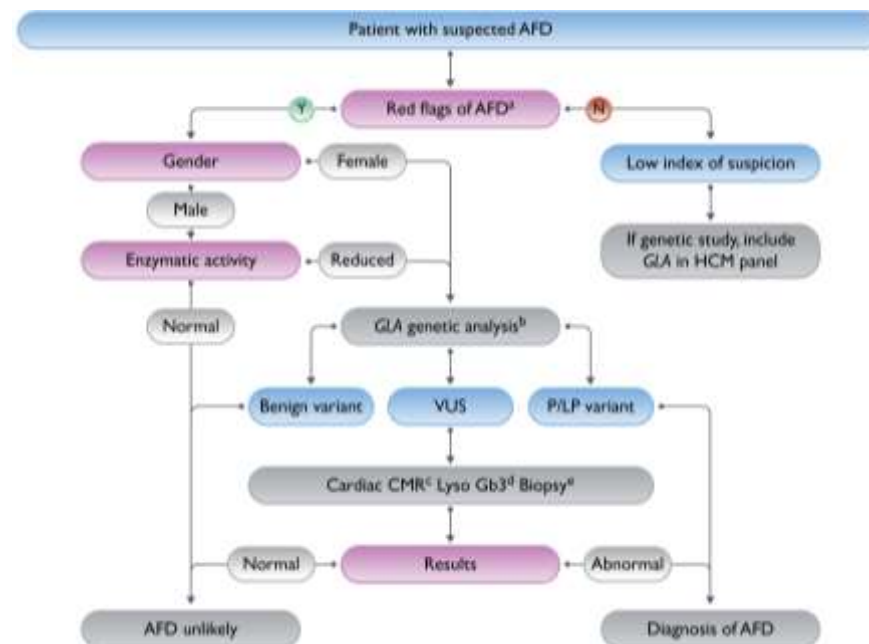


Figure 4-14: Anderson–Fabry disease diagnostic algorithm. α -Gal A, alpha-galactosidase A; AFD, Anderson–Fabry disease; Gb3, globotriaosylceramide; lyso Gb3, globotriaosylsphingosine; P/LP, pathogenic/ likely pathogenic; VUS, variant of unknown significance. **B)** Genetic analysis must include the study of possible large deletions or a copy number variation not detected by the Sanger method. **C)** Low native T1 values reinforce or generate suspicion of Fabry disease. Normal native T1 values do not exclude Fabry disease, as they are rarely observed in untreated patients with mild LVH (mostly females), or in advanced disease due to pseudonormalization. **D)** The finding of increased plasma and/or urinary Gb3, or plasma lyso Gb3 and its analogues in the evaluation of male or female patients with a VUS and normal (in female patients) or lowered α -Gal A activity provides additional diagnostic information, but the role of biomarkers in such patients still requires validation. **E)** An endomyocardial biopsy is recommended, but could be done in other affected organs such as the kidneys and skin. It should be evaluated by expert pathologists and always include electron microscopy studies to detect lamellar bodies and intracellular inclusions. Of note, some drugs may produce drug-induced phospholipidosis with an intracellular accumulation of phospholipids in different organs that can mimic zebra bodies on electron microscopy. **Source:** 2023 ESC Guidelines for the management of cardiomyopathies.

Iron overload cardiomyopathy (IOCM)

- Iron overload results either from genetically determined increased intestinal iron absorption in the context of hereditary haemochromatosis ⁽¹⁾ (primary iron overload) or from multiple blood transfusions required for the management of haematological conditions such as beta-thalassaemia (secondary iron overload).
- In iron overload, the iron binding capacity of transferrin is saturated and non-transferrin-bound iron enters cardiomyocytes through L-type calcium channels, causing oxidative myocardial damage which may have either restrictive or dilated phenotype.
- Early identification and follow-up of cardiac involvement with NT-proBNP levels, echocardiography (particularly tissue Doppler and strain rate) and CMR is highly relevant for the management.
- Myocardial iron deposition can be accurately estimated by the CMR T2* technique; T2* values are correlated with LV/RV systolic function and predict the development of iron-induced HF or arrhythmias.
- Prevention of IOCM is successfully accomplished with iron chelators (e.g deferoxamine, deferiprone, and deferasirox).
- In patients with haemochromatosis, phlebotomy removes 200-250 mg of iron at each session, and should be performed once or twice weekly to reduce serum ferritin to < 1000 ng/mL (or < 1000 µg/L).
Chelation therapy is an effective alternative option when phlebotomy is not feasible, such as in patients with chronic anaemia or malignancy.
- The occurrence of HF portends a poor prognosis, and < 50% of patients with thalassaemia survive up to 5 years following the onset of HF.

Endomyocardial fibrosis

- Endomyocardial fibrosis is the most frequently encountered endomyocardial disorder and is the leading cause of RCM in tropical regions of Africa, Asia and South America.
- Although the aetiology of EMF is still elusive, genetic, dietary, and infectious factors may promote inflammation responsible for endomyocardial damage and fibrosis.

(1) Hemochromatosis is characterized by multi-organ iron deposition leading to infiltrative cardiomyopathy, diabetes, and cirrhosis. Ferritin and iron saturation are elevated.

- The disease affects young and middle-aged individuals, beginning with an active phase of eosinophilic inflammation, followed by scar formation and a high risk for intracavitary thrombosis.
Repeated episodes of active disease lead to a chronic phase, in which RCM prevails, with signs and symptoms of biventricular or right-sided HF.
- The clinical presentation of HF is often dominated by massive ascites, which is out of proportion to peripheral oedema. As a result of increased filling pressures, significant mitral and tricuspid regurgitation and AF are frequently encountered.
- Overt HF carries an ominous prognosis with a 75% mortality rate at 2 years. EMF accounts for 20% of HF hospitalizations and 15% of cardiac deaths in the endemic regions.
- Corticosteroids and immunosuppressive drugs may be used in the early stages of EMF, but there are no randomized trials to support this approach. There is also evidence that cardiac surgery (endocardectomy with or without valve repair/replacement) can increase survival compared with medical treatment.

Loeffler endocarditis

- Hypereosinophilic syndrome (formerly, Loeffler's endocarditis) is secondary to severe systemic eosinophilia (e.g., Churg-and-Strauss disease or systemic parasitic infection).
- Although occurring outside tropical regions, hypereosinophilic syndrome bears a striking resemblance to EMF with respect to the pathogenesis and clinical presentation of RCM.
- It is characterized by persistently elevated eosinophil blood count ($> 1.5 \times 10^9/L$), cardiac morbidity is caused by the release of biologically active substances that damage the endothelium and myocardium with secondary restrictive cardiomyopathy, MR/TR, and cavitory thrombus formation.
- Corticosteroids alone, or in combination with hydroxyurea or interferon- α , during the acute stage of the disease can result in improvement in LVEF and symptoms. Imatinib may be also useful for the treatment of hypereosinophilic syndrome.

N.B:

In a young patient with biventricular thickening and restrictive filling, consider the possibility of Fabry disease, genetic familial amyloidosis, or hypertrophic cardiomyopathy with restrictive phenotype. **MRI** helps in the differential diagnosis and reveals:

- Global subendocardial LGE in amyloidosis.
- Patchy mid-wall enhancement in HCM.
- Patchy mid-wall or subepicardial enhancement in Fabry disease.

RASopathies

- **Definition:** The RASopathies constitute a group of multisystemic syndromes caused by variants in the RAS-mitogen-activated kinase (RAS-MAPK) cascade, including Noonan syndrome, Noonan syndrome with multiple lentigines; Costello syndrome, and cardiofaciocutaneous syndrome.
- **Diagnosis:**
 - The suspicion of an underlying RASopathy should be raised in infant-and childhood-onset HCM with coexisting CHD or extracardiac abnormalities.
 - Gene testing is recommended for diagnosis when phenotypic features are present.
 - Compared with sarcomeric HCM, RASopathy-associated HCM (RAS-HCM) shows earlier age at diagnosis, increased prevalence and severity of left or biventricular obstruction, and higher rates of early hospitalizations for heart failure or need for interventional procedures or surgery.
 - Pulmonary stenosis is the most commonly associated CHD, with a prevalence ranging between 25% and 70%, and unfavourable outcomes for pulmonary valvuloplasty.
- **Management:**
 - Non-vasodilating beta-blockers should be titrated to maximum tolerated dose, particularly in cases of severe biventricular obstruction. Calcium channel blockers may be considered as a second-line option in patients > 6 months of age when beta-blocker therapy is ineffective or not tolerated.
 - Pulmonary valvuloplasty may be considered in children and infants with severe RVOT obstruction.

- Surgical myectomy and orthotopic heart transplantation may be considered.

Friedreich ataxia

- **Definition:** Friedreich ataxia is an autosomal recessive disorder caused by a homozygous GAA triplet repeat expansion in the frataxin (FTX) gene, leading to HCM, progressive neuromuscular symptoms, and extracardiac manifestations, including diabetes mellitus.
- **Diagnosis:**
 - Although several diagnostic criteria have been proposed, genetic testing with identification of bi-co-allelic GAA expansion in the first intron of the FTX gene is required for diagnosis.
 - Cardiovascular involvement usually manifests as HCM, with hypokinetic end-stage disease progression and impaired perfusion reserve, leading to advanced heart failure and death.
 - Supraventricular arrhythmias, particularly AF, are commonly detected. The risk of ventricular arrhythmias and SCD seems low compared with sarcomeric HCM.
 - There is no relationship between the extent of neurological involvement and cardiac phenotype.
 - Mitochondrial iron storage is the pathologic hallmark of the disease.
- **Poor prognostic factors:** The extent of TWI at ECG, LVEF, LV end-diastolic posterior wall thickness, fibrosis on CMR, and hs-TnT.
- **Management:** No specific treatment is currently available. Treatment with idebenone, a coenzyme Q10 analogue, showed the potential to improve LV mass and cardiac outcomes.

Glycogen storage disorders (GSD)

- **Definition:** GSDs represent a heterogeneous group of metabolic diseases, including infantile-onset Pompe disease (GSD, type IIa), Danon disease (GSD, type IIb), and PRKAG2 disease.

- **Diagnosis:**

- A presentation within the first few months of life, hypotonia, failure to thrive, generalized muscle weakness, and severe non-obstructive HCM with concentric pattern followed by hypokinetic end-stage cardiomyopathy, usually within the first year of life, are typical of GSD IIa.
- Short PR interval and increased ECG voltages may represent useful diagnostic clues for GSDs.
- PRKAG2 syndrome should be suspected in the setting of autosomal dominant transmission and association with conduction system disease including ventricular pre-excitation, sick sinus syndrome, AF, AV block, intraventricular conduction delays or sinoatrial blocks.¹
- In Danon disease (GSD IIb): it has X-linked pattern of inheritance. Skeletal myopathy, in association with learning disability, retinal involvement and ventricular pre-excitation, has been detected in males affected by Danon disease, while the cardiac phenotype can be isolated in affected females.
- **Management:** Enzyme replacement therapy is recommended in patients with GSD IIa. To date, there are no approved aetiological therapies for PRKAG2 syndrome and Danon disease.

Inflammatory cardiac diseases

Acute myocarditis

Definition:

Myocarditis is an inflammatory disease of the heart that may occur as a consequence of infections, exposure to toxic substances, and immune system activation.

Aetiology:

- **Infectious (Mostly Viral):** Parvovirus B19, human herpes virus-6, Epstein Barr virus, coxsackie virus, adenovirus, CMV, HIV, SARS-CoV-2, Borrelia, Coxiella burnetii (Q-fever).
- **Auto-immune:** Sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, SLE, ANCA-positive vasculitis, rheumatoid arthritis, any other autoimmune disease
- **Toxins:** Immune check point inhibitors, anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil, Alcohol, amphetamines, cocaine.

Clinical presentation and Prognosis: There are several forms of myocarditis:

- **Subclinical myocarditis** signifies asymptomatic myocarditis (no HF). It is usually self-limited, but a minority of patients develop chronic HF and are diagnosed years later with dilated cardiomyopathy.
- **Clinical myocarditis** implies myocarditis that manifests with HF or pericarditis. It can take several forms:
 - **Mild acute myocarditis** presents with LVEF of 40-50% and sometimes mild HF, along with acute pericarditis signs. It usually recovers, in > 90% of the patients, within weeks or months.
 - **Severe acute or chronic myocarditis** is a myocarditis that manifests as HF or significant LV dysfunction. It reverses in ~35%, significantly improves in ~40%, and progresses to a more severe HF in ~25% of patients. The overall 5-year mortality of patients with persistent HF is similar to idiopathic DCM (~50%).

- **Very severe acute myocarditis** manifests as severe HF of recent onset (typically 2 weeks) with cardiogenic shock or ventricular arrhythmias, usually with a normal-size LV that has not had time to dilate and with severe thickening/edema of the ventricular walls. There are three forms of very severe myocarditis:
 - Eosinophilic hypersensitivity myocarditis: This is a form of myocarditis that occurs as a reaction to drugs (e.g., penicillins, sulfa) and may be accompanied by constitutional symptoms, rash and peripheral eosinophilia. Endomyocardial biopsy shows eosinophilic infiltration. It may be severe but transient and reversible if the drug is withdrawn; corticosteroids may be used.
 - Fulminant lymphocytic myocarditis, in which the patient is unstable acutely but eventually fully recovers if appropriately supported with vasopressors or ventricular assist devices, as the process mainly consists of myocardial depression by cytokines rather than necrosis (long-term prognosis is excellent, with > 90% 10-year survival).
 - Giant-cell myocarditis, in which autoimmune myocardial destruction occurs and the illness continues its aggressive downhill course and intractable ventricular arrhythmias occur. These very severe forms are seen in young patients with aggressive immune systems.

Diagnosis:

| Table 4-20: Diagnostic workup in suspected acute myocarditis | | | |
|---|--|--------------|-------------|
| | | Sensitivity | Specificity |
| Clinical presentation: | | | |
| <i>Acute/new onset chest pain, dyspnoea, signs of left and/or right HF, and/or unexplained arrhythmias or aborted sudden death.</i> | | Low | Low |
| Mandatory diagnostic tests: | | | |
| ECG | <i>New and dynamic ST-T abnormalities, including pseudo-infarct ST elevation, atrial or ventricular arrhythmias, AV blocks, QRS abnormalities.</i> | High | Low |
| Laboratory tests | <i>Elevated troponins with dynamic changes consistent with myocardial necrosis. Routine tests including WBC count to exclude eosinophilia.</i> | Intermediate | Low |

| | | | |
|---|---|--------------|--------------|
| Echocardiography | <i>New structural or function abnormalities not explained by other conditions (e.g., ACS or valvular heart disease):</i> <ul style="list-style-type: none"> - Regional wall motion abnormalities or global ventricular dysfunction - No or mild ventricular dilatation. - Increased wall thickness due to myocardial oedema - Pericardial effusion - Intracardiac thrombi | High | Low |
| CMR | <i>Oedema, inflammation and fibrosis detection, quantification and localization through T1 and T2 mapping, extracellular volume assessment and LGE. (Diagnosis according to Lake Louis criteria)</i> | High | Intermediate |
| Additional diagnostic tests: | | | |
| CA or CTCA | <i>Excludes significant CAD/ACS in suspected myocarditis.</i> | High | High |
| Endomyocardial biopsy ⁽¹⁾ | <i>For diagnosis and indication to specific treatment.</i> | Intermediate | High |
| Cardiac PET | <i>May be useful in patients who cannot undergo CMR or with suspected autoimmune disease or cardiac sarcoidosis.</i> | Low | Low |
| Additional laboratory test | <i>Skeletal muscle enzymes, liver and renal function, natriuretic peptides, thyroid function tests, iron status, markers of systemic autoimmune disease.</i> | Low | Low |
| | <i>CRP elevated in 80-90% patients.</i> | Intermediate | Low |

(1) indicated in case of progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 second-degree or higher AV block with lack of short-term (< 1-2 weeks) expected response to usual medical treatment.

| | | | |
|--|--|-----|-----|
| | <i>PCR testing of common cardiotrophic viruses: can detect systemic infection but does not prove cardiac infection and cannot substitute viral genome analysis on EMB samples.</i> | Low | Low |
|--|--|-----|-----|

Treatment:

- **Hospitalization** for at least 48 h may be useful for patients with acute myocarditis and HF, especially when troponins are elevated and when cardiac dysfunction, and/or arrhythmias are present. Once cardiac enzymes decrease, arrhythmias are absent, and cardiac systolic dysfunction is stabilized, standard HF therapy should be continued for at least 6 months upon complete EF recovery (LVEF > 50%).

- **Immunosuppression** for at least 6-12 months is required in acute myocarditis with clinical or EMB evidence of autoimmune disease, including giant cell myocarditis, acute eosinophilic myocarditis, vasculitis or sarcoidosis and no evidence of active viral infection.

Immunosuppression is not advised on a routine basis without clinical or EMB-based evidence of auto-immune disease.

Initial empirical administration of i.v. corticosteroids may be considered in cases of high suspicion of immune-mediated myocarditis especially if complicated by acute HF, malignant arrhythmias and/or high degree AV block.

- In patients with fulminant myocarditis, **early MCS** should be considered. If myocardial function does not sufficiently recover, longer-term MCS may be required, potentially followed by transplantation.
- Intense sporting activities should be avoided as long as symptoms, cardiac enzymes elevated or ECG/imaging abnormalities are present and last for at least 6 months since complete recovery.
- Yearly follow-up for at least 4 years, with an ECG and echocardiography, is needed.

Management of ventricular arrhythmia and SCD:

- In young people, it is estimated that 2-12% of SCD are related to myocarditis.

- Sustained VAs may occur in acute myocarditis. Tachyarrhythmias were associated with a 2.3-fold increased risk of death. Giant cell myocarditis, although rare, has a higher risk of life-threatening VAs, which are seen in 14% of giant cell myocarditis patients on initial presentation.
- In patients with SMVT of unclear aetiology, myocarditis should be suspected especially when CMR reveals subepicardial and/or intramural abnormal fibrotic myocardial tissue.

| Table 4-21: ESC Recommendations for management of VA and SCD in myocarditis: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| General recommendations: | | |
| <i>In confirmed or clinically suspected acute myocarditis, it is recommended that patients who present with life-threatening VAs are referred to a specialized centre.</i> | I | C |
| Secondary prevention of SCD and treatment of VA: | | |
| <i>ICD implantation</i> | | |
| - <i>is recommended in patients with haemodynamically not-tolerated SMVT in the chronic phase of myocarditis.</i> | I | C |
| - <i>should be considered in haemodynamically tolerated SMVT occurring in the chronic phase of myocarditis.</i> | IIa | C |
| - <i>should be considered during the acute phase of myocarditis before hospital discharge.</i> | IIa | C |
| <i>AADs should be considered (preferably amiodarone and beta-blockers) in patients with symptomatic non-sustained or sustained VAs during the acute phase of myocarditis.</i> | IIa | C |
| <i>In post-myocarditis patients with recurrent, symptomatic VT,</i> | | |
| - <i>AAD treatment should be considered.</i> | IIa | C |
| - <i>Catheter ablation should be considered in whom AADs are ineffective, not tolerated, or not desired.</i> | | |
| <i>In patients with haemodynamically well-tolerated SMVT occurring in the chronic phase of myocarditis, preserved LV function and a limited scar amenable to ablation, catheter ablation may be considered</i> | IIb | C |

as an alternative to ICD therapy, after discussion with the patient and provided that established endpoints have been reached ⁽¹⁾.

Chagas cardiomyopathy

Chagas' disease is the most common cause of non-ischaemic cardiomyopathy in Latin America.

Diagnosis:

- It is due to a parasite (*trypanosoma cruzi*) that is transmitted through the bite of triatomine bug (or “kissing bug”).
- After the incubation period, the vast majority of infected persons have minor or no symptoms, and very few (< 1%) develop acute myocarditis.
- Years later, ~30% develop chronic Chagas disease, which is characterized by a progressive *biventricular failure* and, frequently, a characteristic *large apical aneurysm*.
- Thromboembolic complications, conduction blocks, and arrhythmias are common.
- SCD, particularly due to VF, is the most common cause of death in patients with Chagas' disease. Rassi Score as well as presence of myocardial fibrosis at LGE-CMR are useful in assessing the risk of death.
- The diagnosis is confirmed by serology.

Treatment:

- Beside HF therapy, antiparasitic agents (Benznidazole and nifurtimox) are useful in acute disease and may be useful in slowing the progression of chronic disease, unless severe HF is already present.
- Amiodarone and catheter ablation have been successfully used to control recurrent VAs in some patients.

Table 4-22: ESC Recommendations for management of VA and SCD in Chagas' cardiomyopathy:

(1) VT non-inducibility and elimination of electrograms consistent with conduction delay.

| Recommendations | Class | Level |
|---|------------|----------|
| <i>Amiodarone should be considered to reduce arrhythmia burden in patients with Chagas' cardiomyopathy who present with symptomatic PVCs or VT.</i> | Ila | C |
| <i>In patients with Chagas' cardiomyopathy and recurrent, symptomatic SMVT or ICD shocks for SMVT in whom AADs are ineffective, contraindicated, or not tolerated, catheter ablation in specialized centres should be considered.</i> | Ila | C |
| <i>In patients with Chagas' cardiomyopathy and symptomatic VT in whom AADs (amiodarone and beta-blockers) are ineffective or not tolerated, ICD implantation may be considered.</i> | Ilb | C |

Sarcoidosis

Sarcoidosis is a multisystem inflammatory disease of unknown cause, with a genetic predisposition, characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and non-caseating granulomas leading to tissue scarring.

Pathophysiology:

- Sarcoid cardiomyopathy is characterized by myocardial infiltration with granulomas and edema early on and fibrosis later.
- The LV wall may be thickened by granulomas (RCM which leads to LV diastolic dysfunction); or more commonly thinned by fibrosis with localized aneurysms (DCM which leads to LV systolic dysfunction).
- Clinical presentation depends on the burden and location of granulomatous infiltration, which most commonly affects the LV myocardium. Overt HF is present in 10-40% of patients with cardiac sarcoidosis.
- Sarcoidosis typically involves the **basal septum and lateral LV**, leading to localized akinesis or dyskinesis of these segments. This basal septal involvement leads to infra-His AV block, RBBB, or LBBB, and pseudo-Q waves. VT is also common.

Diagnosis:

- Approximately 20-30% of patients with sarcoidosis have myocardial involvement, but only 5% have clinical myocardial involvement; it usually occurs in conjunction with pulmonary involvement.
- The three usual cardiac manifestations of cardiac sarcoidosis are: LV dysfunction, AV conduction abnormalities, and VAs. Complete AV block develops primarily during the acute inflammatory phase as opposed to sustained VT, which frequently develops in the advanced stage of the disease ⁽¹⁾.
- **Echocardiography** is not very sensitive for detecting the early small granulomas and localized dysfunction. Strain imaging improves its ability to detect myocardial involvement.
- **MRI** finding of LGE at the basal septal and inferolateral walls (subepicardial or mid-wall involvement). A 'hook sign' (or 'hug sign') of septal LGE continuing into the RV free wall has been coined as an imaging biomarker for cardiac sarcoidosis, but an identical pattern can be seen in giant cell myocarditis.
- **¹⁸F-FDG-PET**: A 'hot spot' of ¹⁸F-FDG overlapping a perfusion defect is a characteristic finding ('mismatch pattern'). A 'mismatch pattern' and RV uptake are the key predictors of cardiac events. Atrial uptake portends atrial tachyarrhythmias.
- **Endomyocardial biopsy**: Although confirmation of the diagnosis requires histological evidence of non-caseating granulomas, the sensitivity of EMB is low due to patchy midmyocardial septal infiltration.

N.B: The diagnosis of cardiac sarcoidosis is challenging. It can mimic the ARVC phenotype in the event of a predominant RV involvement or the heart is the only organ affected by sarcoidosis (so-called 'isolated cardiac sarcoidosis'). Cardiac electroanatomical voltage mapping may help in the differential diagnosis between isolated cardiac sarcoidosis and ARVC.

(1) Most VAs in sarcoidosis are scar-related intramural or epicardial substrate (not triggered by active inflammation itself). The VT substrate was more likely located in segments with transmural scar at CMR and lower degree of inflammation on PET-scan.

Treatment:

The current therapeutic options include: HF medication, immunosuppressive agents, and control and prevention of symptomatic VAs and SCD.

- Immunosuppression using steroids is indicated in unequivocal clinical manifestations with evidence of active inflammation on EMB or PET. At an early stage, MRI defects, and myocardial contractility improve with steroids; however, AV block and the risk of VT do not reliably improve with steroids.
- Control and prevention of symptomatic VAs and SCD:
 - Antiarrhythmic drugs, mainly amiodarone or sotalol for VT, are started concomitant with immunosuppression or following an insufficient response.
 - If medical therapy fails, catheter ablation can be considered.
 - ICD is recommended if: **(A)** Prior aborted cardiac arrest, documented spontaneous sustained VT, or LVEF $\leq 35\%$. **(B)** LVEF $> 35\%$ with significant myocardial LGE at CMR after resolution of acute inflammation ⁽¹⁾. **(C)** Inducible sustained monomorphic ventricular arrhythmia at PES in a patient with LVEF 35-50% and minor LGE at CMR.

Prognosis:

- The prognosis of sarcoid cardiomyopathy is similar to idiopathic DCM, and much better than other infiltrative cardiomyopathies (e.g., amyloid).
- Sudden death from VT or conduction blocks is the most common cause of death (30-65% of deaths).
- Poor prognostic factors include: **(1)** Isolated cardiac sarcoidosis, **(2)** LVEF $< 35\%$; **(3)** Documentation of high-degree AV block; and **(4)** Presence of RV or LV scarring at CMR.

(1) A widely accepted definition of significant LGE is not available. LGE in $\geq 9/29$ segments (17 LV and 12 RV segments) and LGE affecting $\geq 22\%$ of the LV mass have been associated with arrhythmic endpoints.

Table 4-23: ESC Recommendations for management of VA and SCD in cardiac sarcoidosis:

| Recommendations | Class | Level |
|---|------------|----------|
| Risk stratification and primary prevention of SCD: | | |
| <i>ICD implantation is recommended in patients with cardiac sarcoidosis who have LVEF \leq 35%.</i> | I | B |
| <i>In patients with cardiac sarcoidosis who have a LVEF 35-50% and minor LGE at CMR, after resolution of acute inflammation, PES for risk stratification should be considered.</i> | IIa | C |
| <i>In patients with cardiac sarcoidosis ICD implantation should be considered in patients:</i> | | |
| - <i>who have an indication for permanent cardiac pacing related to high-degree AV block, regardless of LVEF.</i> | IIa | C |
| - <i>have LVEF > 35% but significant LGE at CMR after resolution of acute inflammation.</i> | IIa | B |
| - <i>Who have LVEF 35-50% and inducible SMVT at PES.</i> | IIa | C |
| Secondary prevention of SCD and treatment of VAs: | | |
| <i>ICD implantation is recommended in patients with cardiac sarcoidosis wh have documented sustained VT, or aborted CA.</i> | I | B |
| <i>In patients with cardiac sarcoidosis and recurrent, symptomatic VA, AAD treatment should be considered.</i> | IIa | C |
| <i>Catheter ablation, in specialized centres, may be considered in cardiac sarcoidosis ICD-recipients with recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated.</i> | IIb | C |

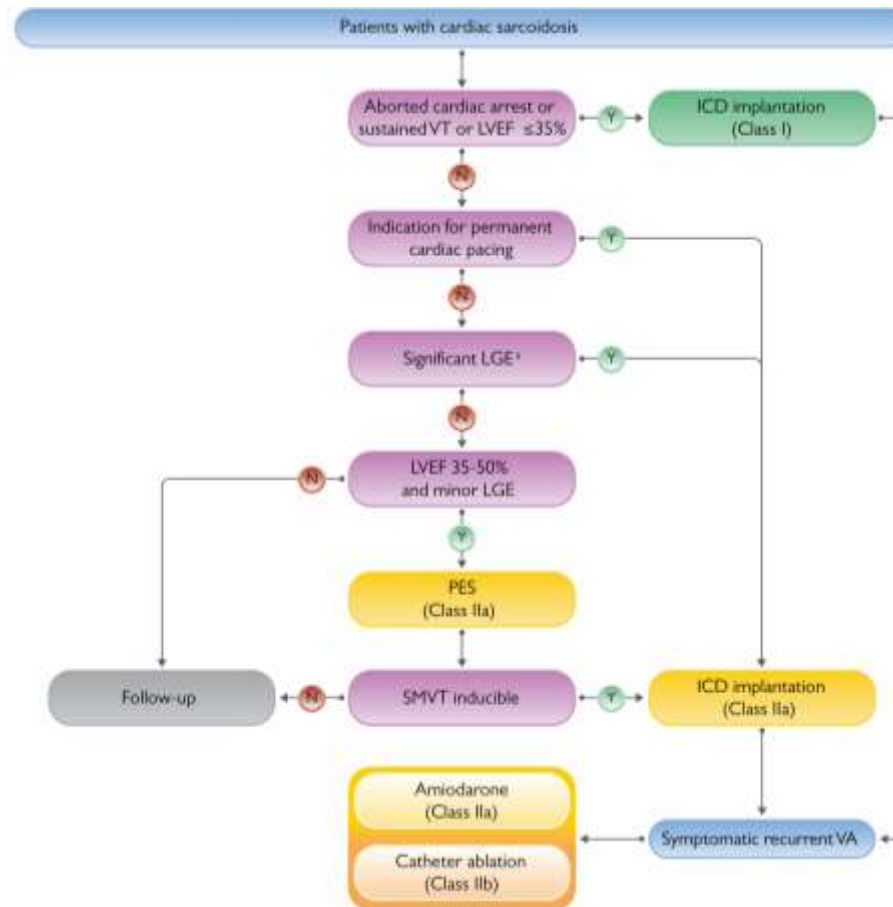


Figure 4-15: Algorithm for sudden cardiac death prevention and treatment of ventricular arrhythmia in patients with cardiac sarcoidosis. (A) LGE affecting $\geq 9/22$ segments or $\geq 22\%$ of the LV mass has been associated with arrhythmic endpoints. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Hypertrophic Cardiomyopathy

Definition:

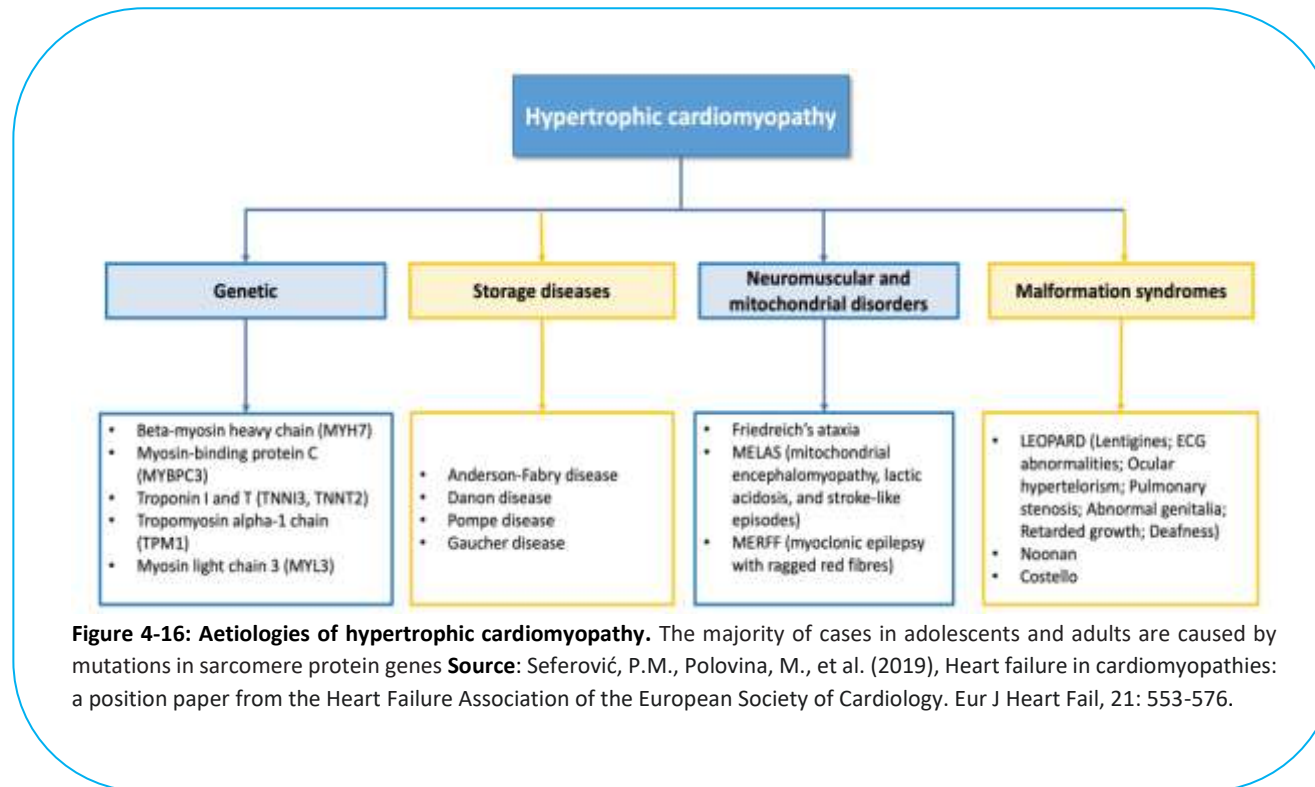
In adults: LVH ≥ 15 mm in one or more LV myocardial segments not sufficiently explained by abnormal loading conditions (no valvular disease, no hypertension, or the degree of hypertrophy is disproportionate to the severity of hypertension). Lesser degrees of wall thickening (13–14 mm) require evaluation of other features including family history, genetic findings, and ECG abnormalities.

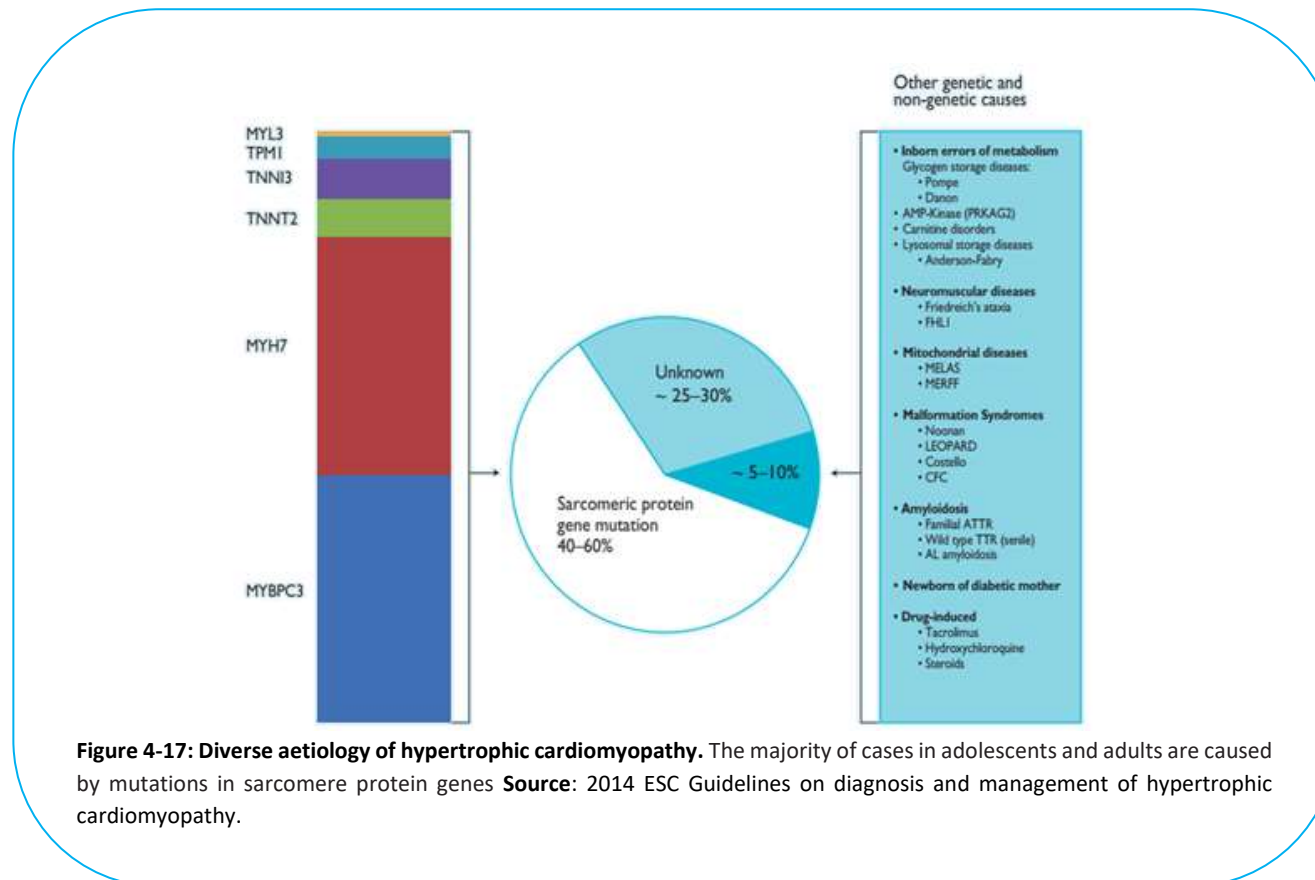
In children: the diagnosis of HCM requires an LV wall thickness more than 2 standard deviations greater than the predicted mean (z-score > 2).

In relatives: the clinical diagnosis of HCM in adult first-degree relatives of patients with unequivocal disease is based on the presence of LV wall thickness ≥ 13 mm.

LVOTO ≥ 30 mmHg at rest or exercise, asymmetric hypertrophy, or increased LGE in a patchy mid-wall pattern in the most hypertrophied segment, further suggest the presence of HCM.

It can be considered familial when two or more first- or second-degree relatives with HCM or a first-degree relative with autopsy proven HCM and sudden death at < 50 years of age are detected.





Features of HCM:

- **Asymmetry:**
 - Hypertrophy most often involves two or more myocardial segments in an asymmetric and sometimes “bumpy” fashion, but may involve only one segment.

- The hypertrophy is usually asymmetric and involves the septum and the anterolateral wall with a septal-to-posterior wall thickness ratio of $> 1.3:1$ (more specifically $> 1.5:1$), but it may be symmetric and diffuse. The posterior wall is the site least frequently thickened in HCM.
- Severe LVOT obstruction leads to severe afterload elevation that may result in a global LVH with time; hence, septal reduction not only reduces septal thickness but also the LV thickness at distant segments.
- **Pattern of LVH in HCM:**
 - Sigmoid HCM (40-50%): septal protuberance basal concave septum
 - Reverse Curve HCM (30-40%): convex septum, concentric LV cavity.
 - Apical HCM (10%): apical hypertrophy “Ace of spades”.
 - Neutral HCM (10%): straight septum.
- **LVOT obstruction:**
 - Approximately 40-70% of patients have an obstructive HCM, diagnosed by a LV intracavitary gradient ≥ 30 mmHg at rest ($\sim 25\%$ of patients) or during exercise. Non-obstructive HCM, demonstrating gradients < 30 mmHg at rest and/or with exercise, is present in 30–60% patients. When obstructive, HCM is called hypertrophic obstructive cardiomyopathy (HOCM).
 - The increased velocity across the LVOT draws the anterior mitral leaflet and its chordae during systole (venturi effect), which further narrows the LVOT and creates LVOT obstruction. This process is called systolic anterior motion (SAM) of the anterior leaflet (both the leaflet edge and chordae).
 - The gradient is within the LV, i.e., pressure is elevated throughout the LV body and a portion of the LVOT then drops at one point in the LVOT rather than across the aortic valve.
 - On echo-Doppler, the velocity is increased across the point of LVOT obstruction and is decreased proximal to this point (LV inflow and mid-LV cavity) and distal to this point (aortic valve).
 - The marked septal hypertrophy may also contribute to RVOT obstruction, particularly in children.
 - LVOT obstruction is associated with more symptoms and a higher HF-related mortality, but only a weak correlation with sudden death.

○ **Causes of MR in HOCM:**

- **MR related to SAM:** MR is mainly related to SAM; it is directed posteriorly and peaks in mid and late systole. The severity of MR correlates with the severity of the LVOT gradient. MR may be severe (in ~10%) if the posterior leaflet is not elongated enough to meet with the “sucked” anterior leaflet. Severe MR with a relatively short posterior leaflet is expected to improve after myectomy.

- **Mitral valve abnormalities aggravate SAM and LVOT obstruction:**

A. Anterior leaflet elongation > 30 mm, which provides extra slack and facilitates SAM and LVOTO.

B. Central/anterior papillary muscle malposition (as opposed to anterolateral position).

C. Chordal insertion at the base rather than the tip of the anterior leaflet.

(B) and **(C)** lead to tenting of the anterior leaflet anteriorly, into the LVOT stream.

- **MR due to structural valvular abnormalities:** Some primary valvular abnormalities can cause MR independent of SAM, and these are seen in 10-20% of HOCM.

This primary MR is characterized by a central or anteriorly directed jet that is usually holosystolic and is not expected to resolve with septal reduction. Severe MR despite an elongated posterior leaflet, or central or anteriorly directed MR, is concerning for a structural mitral abnormality. These abnormalities include:

- Extreme elongation and prolapse of the posterior mitral leaflet (~9% of operated HOCM).
- Papillary muscle insertion directly onto the anterior leaflet.
- Chordal rupture.

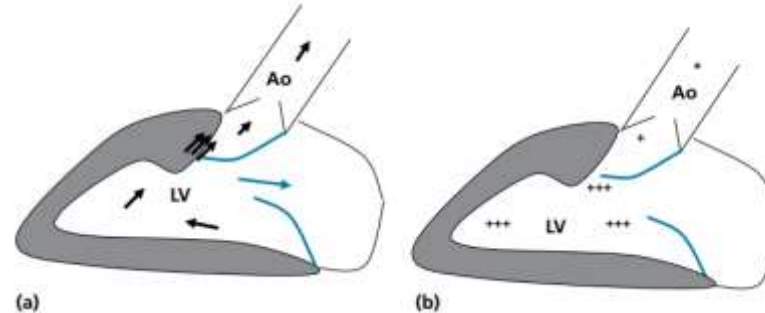


Figure 4-18: (A) Asymmetric septal hypertrophy with increased velocity across the LVOT (3 arrows). This increased systolic velocity creates a Venturi effect that pulls the anterior mitral leaflet (SAM) and creates LVOT obstruction as well as a posteriorly directed MR (blue arrow). Pulsed-wave Doppler should be used to sequentially interrogate the LV from apex up to the LVOT in order to confirm the anatomical level of obstruction. Note the normal velocity across the LV body, LVOT proximal to the obstruction and distal to it, and aorta (single arrows). **(B) Pressure is increased throughout LV inflow, LV body, LVOT (+++),** and drops beyond the LVOT obstruction (+). Even pressure at the mitral valve level (inflow tract pressure) is elevated. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Less common forms of HCM:

- **Mid-cavitary HCM** consists of thickening of the mid-portion of the LV, associated with apical thinning and aneurysm formation, simulating apical MI; the hypertrophy was probably more diffuse, but the apex infarcted as a result of the severe pressure rise and diffusely increased O₂ demands that accompanied cavity obliteration. This form of HCM has a particularly unfavorable prognosis with a high risk of sudden death and LV thrombus. Mid-cavitary HCM may also be due to anomalous basal position of the anterior papillary muscle that inserts directly onto the anterior leaflet.
- **Apical HCM** is a common form of HCM in the Asian population. It was considered entirely benign, but recent data suggests a yearly mortality of 0.5-4%, approaching that of classic HCM. It may evolve into an apical aneurysm.

Pathophysiology of heart failure in HCM:

- **HCM due to sarcomere gene mutations:**

- In genetic HCM, excessive energy utilization required to generate hyperdynamic isokinetic tension within the sarcomere result in *myocyte hypertrophy and disarray*.
- Compromised energy balance, higher oxygen demand of the hypertrophied myocardium and coronary microvascular dysfunction, result in recurrent episodes of *demand ischaemia* (e.g., during exercise or tachycardia) that can explain symptoms of chest pain, exercise intolerance and exertional dyspnoea.
- Impaired termination of contraction at low intracellular Ca^{2+} produces incomplete myocyte relaxation and *diastolic dysfunction*, which may precede and follow the development of overt hypertrophy.
- In patients with obstructive HCM, the severity of HF is principally determined by pressure overload imposed by dynamic obstruction to LV outflow during systole. It is caused by the septal hypertrophy, abnormal SAM of the mitral valve, and abnormal apposition of the hypertrophied septum and anterolateral papillary muscle (5-10%).
- LV diastolic dysfunction represents another important mechanism underlying the development of HF (i.e. HFpEF) in HCM. It is present in the majority of patients, irrespective of intracavitary obstruction.
- In addition, mitral valve abnormalities, coronary myocardial bridging, apical aneurysms, atrial remodelling and autonomic dysfunction may contribute to the development and severity of HF.
- **HCM due to storage disorders:**
 - HCM caused by rare storage disorders (e.g., Anderson-Fabry, Danon and Pompe diseases), HF most commonly takes the HFpEF phenotype due to an extensive, concentric LVH. The increased wall thickness is caused partly by myocyte hypertrophy (due to lysosomal accumulation of glycosphingolipids), and partly by interstitial fibrosis stimulated by overproduction of profibrotic cytokines. Asymmetric LVH in storage disorders is rare, while biventricular hypertrophy may occur in up to 25% of patients.
 - Rarely, diastolic dysfunction in storage disorders may progress to a restrictive filling pattern, accompanied by a significant biatrial enlargement. Thus, storage disorders need to be considered as underlying aetiology of both HCM and RCM.
 - Development of LV systolic dysfunction and HFrEF invariably occurs in Danon disease and occasionally in patients with other metabolic cardiomyopathies.

Natural history and mortality:

○ **HCM due to sarcomere gene mutations:**

- Typically, LVH in HCM caused by sarcomere disorders develops in adolescence or early adulthood (although it may present from early childhood to the seventh decade), and remains stable with preserved LV systolic function and variable degrees of LV diastolic dysfunction.

Severe diastolic dysfunction (i.e., restrictive pattern) can be demonstrated in up to 9.2% of patients with HCM. These patients generally present with symptoms of low cardiac output (rather than with overt congestion), and they have an independently increased risk of progression to advanced HF.

- **In patients with obstructive HCM**, the severity and prognosis of HF are principally influenced by LVOT obstruction. The gradient is strongly associated with symptom progression and CV mortality secondary to HF and stroke (AF). Mid-cavity obstruction is often accompanied by severe HF symptoms and impaired survival.
- **In patients with non-obstructive HCM**, the disease usually has a benign and stable course. However, Approximately 5% of patients eventually succumb to this chronically elevated afterload and develop LV dilatation with reduced systolic function (burned-out HCM) which carries a considerable risk of mortality (11% per year).

○ **HCM due to storage disorders:**

- HF may become apparent at any time from childhood to the mature age depending on the extent of cardiac involvement, in relation to the severity of enzyme deficit.
- Increased levels of cardiac biomarkers (Troponin T, NT-proBNP) and higher extent of fibrosis have been associated with a reduction in LVEF during the follow-up.
- Cardiac disease may progress to LV systolic dysfunction and HFrEF in 6–8% (in particular in the absence of enzyme replacement therapy) and confers a great risk of HF-related mortality.

Diagnosis:

■ **Symptoms:**

- Most patients are asymptomatic and have a normal lifespan.
- **Dyspnea and HF** may result from LVOT obstruction and/or LV diastolic dysfunction.
Severe functional limitation (class III or IV) is uncommon but may eventually develop in up to 45% of patients with LVOT obstruction, over the course of 10-year follow-up. Conversely, up to 23% of patients may have a paradoxical reduction of gradient with exercise, which partly explains how some patients are asymptomatic.
- **Angina** may result from increased demands and from the elevated LVEDP, which impairs coronary microcirculatory flow. Myocardial bridging is also common and may contribute to ischemia.
- **Syncope:** Two types of syncope must be distinguished:
 - **Exertional syncope** is more ominous and occurs secondary to arrhythmia (e.g., VT or AF) or dynamic LVOT obstruction that worsens with exertion.
 - **Post-exertional syncope:** in the post-exertional phase, the reduced peripheral venous pumping reduces venous return to the hypercontractile LV. This increases LVOT obstruction and may lead to syncope, but may also activate the myocardial C receptors of the small hypercontractile cavity, leading to a vasovagal syncope. Syncope occurring in these contexts is not associated with an increased risk of SCD.
- **SCD** is often the first manifestation in ~ 70% of patients. SCD often occurs at rest or with mild activities, but 15% of SCDs occur during moderate or heavy activity (relatively more so in athletes).
- A number of noncardiac symptoms act as pointers for specific diagnoses.

Table 4-24: ESC Recommendations for the assessment of symptoms related to HCM:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|----------------------------------|--------------|--------------|
| Assessment of chest Pain: | | |

| | | |
|--|------------|----------|
| <i>Invasive coronary angiography is recommended in adult survivors of cardiac arrest, in patients with sustained ventricular tachyarrhythmia and in patients with severe stable angina CCS class ≥ 3</i> | I | C |
| <i>Invasive or CT coronary angiography should be considered in:</i> <ul style="list-style-type: none"> - <i>Patients with typical exertional chest pain (CCS Class < 3) who have an intermediate pre-test probability of atherosclerotic coronary artery disease based on age, gender and risk factors for atherosclerosis, or a history of coronary revascularization.</i> - <i>All patients aged ≥ 40 years, before septal reduction therapy, irrespective of the presence of typical exertional chest pain.</i> | IIa | C |
| Assessment of Heart Failure: | | |
| <i>Cardiac catheterization -to evaluate right and left heart function and pulmonary arterial resistance- is recommended in patients being considered for heart transplantation or mechanical circulatory support.</i> | I | B |
| <i>In symptomatic patients with inconclusive, non-invasive cardiac imaging, left and right heart catheterization may be considered, to assess the severity of LVOTO and to measure LV filling pressures.</i> | IIb | C |
| <i>Cardiopulmonary exercise testing, with simultaneous measurement of respiratory gases, is recommended in severely symptomatic patients with systolic and/or diastolic LV dysfunction being evaluated for heart transplantation or mechanical support</i> | I | B |
| <i>Irrespective of symptoms, cardiopulmonary exercise testing with simultaneous measurement of respiratory gases (or standard treadmill or bicycle ergometry when unavailable) should be considered to assess the severity and mechanism of exercise intolerance and change in systolic blood pressure.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>Cardiopulmonary exercise testing, with simultaneous measurement of respiratory gases (or standard treadmill or bicycle ergometry when unavailable), should be considered in symptomatic patients undergoing septal alcohol ablation and septal myectomy to determine the severity of exercise limitation.</i> | IIa | C |
| Assessment of Syncope: | | |
| <i>12-lead ECG, upright exercise test, resting and exercise 2D and Doppler echocardiography, and 48- hour ambulatory ECG monitoring are recommended in patients with unexplained syncope, to identify the cause of their symptoms.</i> | I | C |
| <i>An Implantable Loop Recorder (ILR) should be considered in patients with recurrent episodes of unexplained syncope, who are at low risk of SCD.</i> | IIa | C |
| Assessment of palpitation: | | |
| <i>For patients with frequent or sustained palpitations, 48-hour ambulatory ECG monitoring is recommended, to identify the likely cause.</i> | I | C |
| <i>An ILR may be considered for patients with frequent palpitations, in whom no cause is identified following prolonged ECG monitoring.</i> | IIb | C |
| <i>Invasive electrophysiological study is recommended in patients with documented persistent or recurrent supraventricular tachycardia and in patients with ventricular pre-excitation, in order to identify and treat an ablatable substrate.</i> | I | C |
| <i>Invasive electrophysiological study may be considered in selected patients with documented, symptomatic, monomorphic, sustained (> 30 s) ventricular tachycardia in order to identify and treat an ablatable arrhythmia substrate.</i> | IIb | C |
| <i>Invasive electrophysiological study with programmed ventricular stimulation is not recommended for sudden cardiac death risk stratification.</i> | III | C |

- **ECG findings:** shows LVH voltage with a strain pattern, and/or deep T-wave inversion in leads V₂–V₆ even without LVH voltage. Prominent septal depolarization may lead to large Q waves in the lateral and inferior leads (pseudoinfarct pattern). Approximately 10% of HCM patients have a normal ECG, which is a limitation of pre-athletic ECG screening.

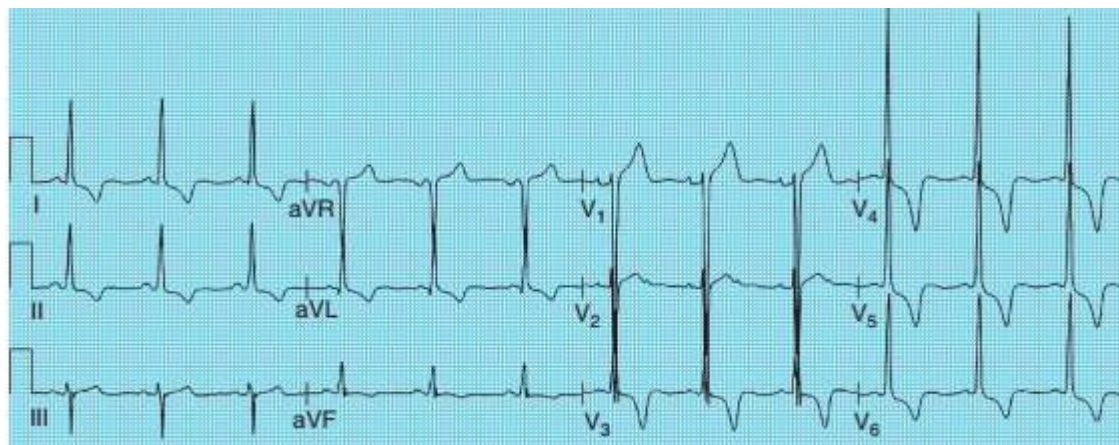


Figure 4-19: Hypertrophic Cardiomyopathy. This 12-lead ECG with rhythm strips shows sinus rhythm with marked left ventricular hypertrophy and associated ST-T abnormalities. These findings in a young patient with syncope suggest the diagnosis of hypertrophic cardiomyopathy, which was confirmed by echocardiography. **Source:** Olshansky, Brian, et al. *Arrhythmia Essentials*. Elsevier, 2017.

Table 4-25: ESC Recommendations on ECG in HCM:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with HCM, a 12-lead ECG is recommended in the initial evaluation and as part of periodic follow-up (every 1 to 2 years)</i> | I | B |
| <i>In first-degree relatives of patients with HCM, a 12-lead ECG is recommended as a component of the screening algorithm.</i> | I | B |

| | | |
|--|------------|----------|
| <i>48-hour ambulatory ECG monitoring is recommended in patients at their initial clinical assessment, to detect atrial and ventricular arrhythmia.</i> | I | B |
| <i>In patients with HCM, 24- to 48-hour ambulatory ECG monitoring is recommended in the initial evaluation and as part of periodic follow-up (every 1 to 2 years) to identify patients who are at risk for SCD and guide management of arrhythmias.</i> | I | B |
| <i>In patients with HCM who develop palpitations or lightheadedness, extended (> 24 hours) ECG monitoring or event recording is recommended, which should not be considered diagnostic unless patients have had symptoms while being monitored.</i> | I | B |
| <i>In patients with HCM who have additional risk factors for AF, such as LA dilatation, advanced age, and NYHA class III to class IV HF, and who are eligible for anticoagulation, extended ambulatory monitoring is reasonable to screen for AF as part of initial evaluation and periodic follow-up (every 1 to 2 years)</i> | IIa | B |
| <i>In adult patients with HCM without risk factors for AF and who are eligible for anticoagulation, extended ambulatory monitoring may be considered to assess for asymptomatic paroxysmal AF as part of initial evaluation and periodic follow-up (every 1 to 2 years).</i> | IIb | B |

▪ **Imaging evaluation:**

• **For diagnosis and assessment of HCM:**

- *Asymmetric LV hypertrophy:* Wall thickness ≥ 15 mm in one or more LV myocardial segments in adults and more than two standard deviations greater than the predicted mean in the children.
- The obstructive form of HCM is characterized by SAM. SAM is seen on the parasternal long-axis view and on the M-mode of the mitral valve. The greater the degree and duration of mitral-septal contact (e.g., > 30% of systole), the more severe the obstruction.
- In addition, M-mode of the aortic valve shows *mid-systolic closure* due to the mid-systolic obstruction.
- *LA enlargement* is universal in HCM (a normal LA size makes HCM unlikely).

- *Localization of the obstruction:* Pulsed-wave Doppler interrogation reveals that the velocity is increased across one point in the LVOT, but is normal (~1m/s) or low in the LV body and distally across the aortic valve. However, the velocity may also increase in the LV body when hypertrophy is generalized with cavity obliteration, even if the obstruction is mainly at the LVOT level. The LVOT gradient is late peaking, with a “*dagger*” shape on spectral Doppler. It is dynamic and may be unveiled or worsened by Valsalva maneuver, which should be performed in all cases of HCM. Aliasing typically occurs across the point of LVOT obstruction rather than the aortic valve.
- After localizing the site of obstruction with PW Doppler, *Continuous-wave Doppler* is required to capture the actual velocity.

- **For detection of the Aetiology:**

| Table 4-26: Echocardiographic features that suggest specific aetiologies: | |
|---|--|
| Finding | Specific disease to be considered |
| <i>Increased interatrial septum thickness</i> | <i>Amyloidosis</i> |
| <i>Increased AV valve thickness</i> | <i>Amyloidosis; Anderson-Fabry disease</i> |
| <i>Increased RV free wall thickness</i> | <i>Amyloidosis, Fabry disease, Noonan syndrome</i> |
| <i>Mild to moderate pericardial effusion</i> | <i>Amyloidosis, myocarditis</i> |
| <i>Ground-glass appearance of ventricular myocardium</i> | <i>Amyloidosis</i> |
| <i>Concentric LVH</i> | <i>Glycogen storage disease, Anderson Fabry disease, PRKAG2 mutations</i> |
| <i>Extreme concentric LVH (wall thickness ≥ 30 mm)</i> | <i>Danon disease, Pompe disease</i> |
| <i>Global LV hypokinesia (with or without LV dilatation)</i> | <i>Mitochondrial disease, TTR-amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease</i> |

| | |
|--|---|
| <i>RVOT obstruction</i> | <i>Noonan syndrome and associated disorders</i> |
| <i>Apical sparing pattern on longitudinal strain imaging</i> | <i>Amyloidosis</i> |

- **To guide the treatment:**

- Intracoronary contrast echocardiography (TTE, TOE) is recommended in all patients undergoing alcoholic septal ablation, to ensure correct localization of alcohol.
- Perioperative TOE is recommended in patients undergoing septal myectomy, to guide the surgical strategy, to assess post-surgical complications and to detect residual LVOT obstruction.

| Table 4-27: ESC Recommendations for imaging and biopsy evaluation in HCM: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Transthoracic echocardiography: | | |
| <i>In all patients with HCM at initial evaluation, transthoracic 2D and Doppler echocardiography are recommended, at rest and during Valsalva manoeuvre in the sitting and semi-supine positions and then on standing if no gradient is provoked.</i> | I | B |
| <i>Measurement of maximum diastolic wall thickness is recommended, using 2D short-axis views in all LV segments, from base to apex.</i> | I | C |
| <i>A comprehensive evaluation of LV diastolic function is recommended, including pulsed Doppler of mitral valve inflow, tissue Doppler velocities at the mitral annulus, pulmonary vein flow velocities, PA systolic pressure, and measurement of LA size and volume.</i> | I | C |
| <i>In symptomatic patients with a resting or provoked peak instantaneous LVOT gradient < 50 mmHg, 2D and Doppler echocardiography during exercise in the standing, sitting or semi-supine position is recommended to detect provokable LVOTO and exercise-induced mitral regurgitation.</i> | I | B |

| | | |
|---|------------|----------|
| <i>In asymptomatic patients with a resting or provoked peak instantaneous LV outflow tract gradient < 50 mmHg, 2D and Doppler echocardiography during exercise -in the standing, sitting or semi-supine positions- may be considered when the presence of an LVOT gradient is relevant to lifestyle advice and decisions on medical treatment.</i> | IIb | C |
| <i>In patients with sub-optimal images or with suspected LV apical hypertrophy or aneurysm, TTE with LV cavity opacification -using intravenous echocardiographic contrast agents- should be considered as an alternative to CMR imaging.</i> | IIa | C |
| <i>Intracoronary contrast echocardiography is recommended in all patients undergoing alcoholic septal ablation, to ensure correct localization of alcohol.</i> | I | B |
| Transesophageal echocardiography: | | |
| <i>TOE should be considered in patients with LVOTO if the mechanism is unclear, or when assessing the mitral valve apparatus before a septal reduction procedure, or when severe mitral regurgitation, caused by intrinsic valve abnormalities, is suspected.</i> | IIa | C |
| <i>Perioperative TOE is recommended in patients undergoing septal myectomy, to confirm the mechanism of LVOTO, to guide the surgical strategy, to assess post-surgical complications and to detect residual LV outflow tract obstruction.</i> | I | C |
| <i>TOE with intracoronary contrast injection of the candidate septal perforator artery should be considered to guide septal alcohol ablation when transthoracic windows are insufficient for proper visualization of echo-contrast within the myocardium.</i> | IIa | C |
| Cardiac MRI: | | |
| LGE is present in 65% of patients, typically in a patchy mid-wall pattern in areas of hypertrophy and at the anterior and posterior RV insertion points. LGE is unusual in non-hypertrophied segments except in advanced stages of disease, when full-thickness LGE in association with wall thinning is common. LGE may be absent in people with HCM, particularly young people and those with mild disease. | | |

| | | |
|---|--|--------------------------------------|
| <i>In the absence of contraindications, CMR with LGE is recommended in patients with suspected HCM who have inadequate echocardiographic windows, in order to confirm the diagnosis.</i> | I | B |
| <i>In the absence of contraindications, CMR with LGE should be considered in:</i> <ul style="list-style-type: none"> - <i>Patients fulfilling diagnostic criteria for HCM, to assess cardiac anatomy, ventricular function, and the presence and extent of myocardial fibrosis.</i> - <i>Patients with suspected apical hypertrophy or aneurysm.</i> - <i>Patients with suspected cardiac amyloidosis.</i> | IIa IIa IIa | B C C |
| <i>CMR with LGE may be considered before septal alcohol ablation or myectomy, to assess the extent and distribution of hypertrophy and myocardial fibrosis.</i> | IIb | C |
| <i>For patients with HCM, repeat contrast enhanced CMR imaging on a periodic basis (every 3 to 5 years) for the purpose of SCD risk stratification may be considered to evaluate changes in LGE and other morphologic changes, including EF, development of apical aneurysm, or LV wall thickness.</i> | IIb | C |
| Nuclear imaging and CT: | | |
| <i>The major contribution of nuclear imaging in HCM is the detection of TTR-related cardiac amyloidosis.</i> | | |
| <i>Bone scintigraphy (particularly with ^{99m}Tc-DPD) should be considered in patients with symptoms, signs and non-invasive tests consistent with TTR-related amyloidosis.</i> | IIa | B |
| <i>Cardiac CT should be considered in patients who have inadequate echocardiographic imaging and contraindications for CMR.</i> | IIa | C |
| Endomyocardial biopsy: | | |

Endomyocardial biopsy may be considered when the results of other clinical assessments suggest myocardial infiltration, inflammation or storage that cannot be confirmed by other means.

| | |
|------------|----------|
| IIb | C |
|------------|----------|

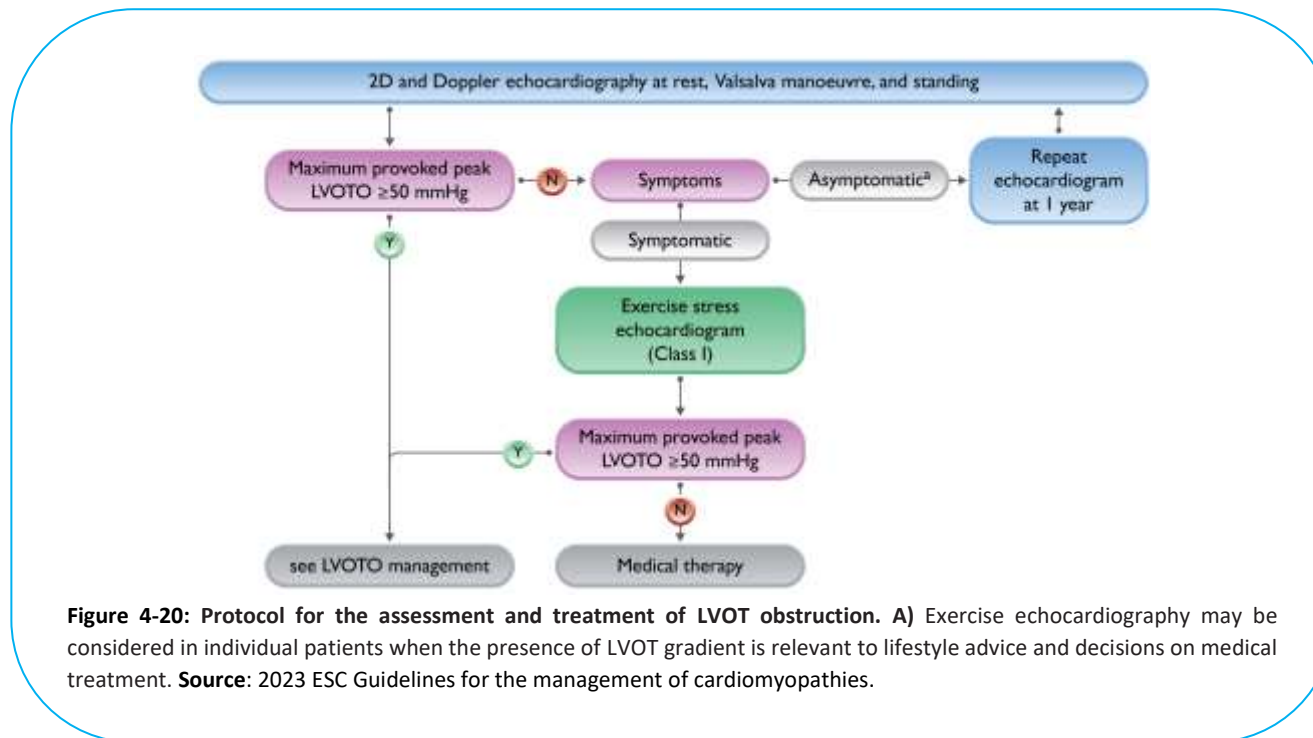
▪ **Exercise Stress testing:**

- Patients without any gradient at rest may develop a significant gradient with maneuvers. The gradient increases with decreased preload (Valsalva maneuver, hypovolemia, nitroglycerin), decreased afterload (vasodilators), or increased inotropism (exercise, inotropic drugs e.g dobutamine ⁽¹⁾). Each of these changes results in closer approximation of the ventricular septum and anterior mitral leaflet during systole. Physiological maneuvers rather than pharmacological interventions should be used to assess provokable gradient (exercise, Valsalva). Valsalva elicits gradients in only 50% of patients with exertional gradients. Thus, in a patient with exertional symptoms, exercise echo is warranted for gradient provocation if Valsalva is negative.
- There is evidence to show that exercise stress testing (particularly cardiopulmonary exercise test), is safe in patients with HCM and provides information on the severity and mechanism of functional limitation. The value of exercise testing in assessing myocardial ischemia is limited because of resting ECG and wall motion abnormalities. Myocardial perfusion imaging using single-photon or positron emission tomography shows perfusion abnormalities in > 50% of patients, most of whom have no significant epicardial CAD.

| Table 4-28: AHA/ACC Recommendations on Exercise stress testing: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |

(1) *Dobutamine-induced gradient does not necessarily imply exertional gradient and should not be used to diagnose HOCM. In fact, exercise increases myocardial contractility but also preload, which reduces cavity obliteration and the potential for intracavitary obstruction; dobutamine increases myocardial contractility but does not increase preload, and thus more readily creates intracavitary obstruction even in the absence of HOCM.*

| | | |
|--|------------|----------|
| <i>For symptomatic patients with HCM who do not have resting or provokable outflow tract gradient ≥ 50 mmHg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO.</i> | I | B |
| <i>In patients with non-obstructive HCM and advanced HF (NYHA class III to IV despite GDMT), cardiopulmonary exercise stress testing should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support.</i> | I | B |
| <i>In patients with HCM, exercise stress testing is reasonable to determine functional capacity and to provide prognostic information as part of initial evaluation.</i> | IIa | B |
| <i>For asymptomatic patients with HCM who do not have a resting or provokable outflow tract gradient ≥ 50 mmHg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO.</i> | IIa | C |
| <i>In patients with obstructive HCM who are being considered for SRT and in whom functional capacity or symptom status is uncertain, exercise stress testing may be reasonable.</i> | IIb | C |
| <i>In patients with HCM in whom functional capacity or symptom status is uncertain, exercise stress testing may be considered every 2 to 3 years.</i> | IIb | C |



■ **Laboratory tests:**

| Table 4-29: Recommended laboratory tests in adult patients with HCM: | |
|--|---|
| Test | Comment |
| Haemoglobin | <i>Anaemia exacerbates chest pain and dyspnoea and should be excluded.</i> |
| Renal function | <i>Renal function may be impaired in patients with severe LV impairment. Impaired GFR and proteinuria may be seen in amyloidosis, Anderson-Fabry disease and mitochondrial DNA disorders.</i> |

| | |
|--|--|
| Liver transaminases | <i>Liver tests may be abnormal in mitochondrial disorders, Danon disease and β-oxidation defects.</i> |
| Creatine phosphokinase | <i>CPK is raised in metabolic disorders such as Danon and mitochondrial disease.</i> |
| Plasma/leucocyte alpha galactosidase A (in men > 30 years) | <i>Low (< 10% normal values) or undetectable in male patients with Fabry disease. Plasma and leucocyte enzyme levels are often within the normal range in affected females, so genetic testing may be considered if clinically suspected.</i> |
| Serum free light chain, serum and urine urine electrophoresis | <i>Should be considered if amyloidosis is suspected from history and non-invasive tests. Confirmation of the diagnosis usually requires histological analysis.</i> |
| Fasting glucose | <i>May be elevated in some mitochondrial DNA disorders. May be low in fatty acid and carnitine disorders.</i> |
| Brain natriuretic peptide and troponin T | <i>Elevated plasma levels of BNP, NT-proBNP and troponin T are associated with higher risk of CV events, heart failure and death.</i> |
| Thyroid function tests | <i>Should be measured every 6 months in patients treated with amiodarone.</i> |
| Plasma Lactate | <i>Elevated in some patients with mitochondrial disorders (MELAS).</i> |

▪ **Invasive hemodynamic findings:**

- In the presence of a gradient between the LV and aorta and if HOCM is suspected, use an end-hole catheter, rather than a multihole catheter, and slowly pull back across the LVOT to localize the site of pressure drop. In addition to the subaortic pressure gradient, the aortic and LV pressure tracings are characterized by the following:
- Systolic aortic pressure has an early “spike” and a late “dome” (“spike and dome” appearance). In fact, LVOT obstruction is dynamic and is less severe in early systole when LV volume is largest, allowing a “peak” in aortic pressure. Obstruction is worst in mid- and late systole when LV volume is reduced, explaining the late “dome.”
- Since LV obstruction is worst in late systole, LV pressure proximal to the obstruction peaks late and has a late-peaking “dagger” shape (similar to the spectral Doppler “dagger” shape velocity across the LV).
- Pressure gradient is dynamic with provocative maneuvers. Being dynamic, the gradient may be labile and varies with changes of loading conditions.

• **After a premature beat:**

- LV volume increases, but LV contractility increases even more and overwhelms the benefit derived from LV volume, producing an increase in LVOT obstruction. LV pressure increases but the stroke volume decreases, and thus the aortic pulse pressure decreases (Brockenbrough phenomenon); the aortic systolic pressure decreases as well.
- This contrasts with AS, wherein the fixed obstruction does not prevent the increase in stroke volume and aortic pulse pressure after a premature beat; the gradient increases with the increase in flow, as per Gorlin’s equation, but the aortic pressure increases as well.
- In both HOCM and AS, the gradient and the murmur increase after a premature beat, but more so in HOCM, and the pulse only decreases in HOCM.

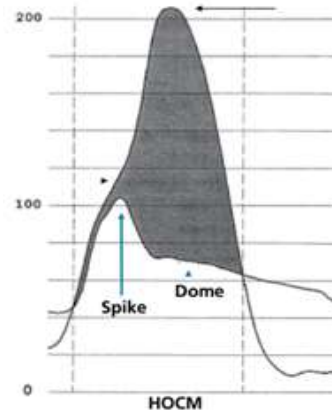


Figure 4-21: HOCM hemodynamics. The LVOT obstruction worsens throughout systole as the LV becomes smaller. The aortic pressure peaks in the early systole (*blue vertical arrow*); then LVOT obstruction worsens, so the LV pressure tracing “bends” (*black arrowhead*) then peaks in mid- to late systole (*horizontal arrow*) while the aortic systolic pressure adopts a “dome” appearance. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

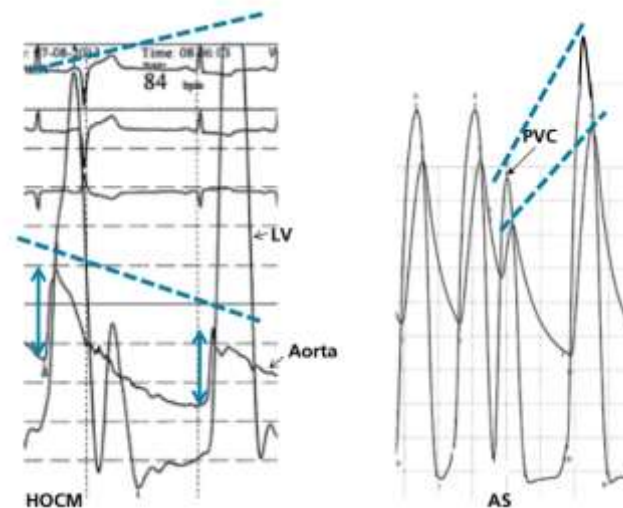


Figure 4-22: Brockenbrough phenomenon after a premature beat in HOCM. Note the increase in pressure gradient (*interrupted lines*) but the reduction in aortic pulse pressure (*double arrows*) after a pause in HOCM, vs. the increase in pressure gradient with an increase in aortic pulse pressure in AS. Note the “spike and dome” appearance of the aortic pressure in HOCM, which becomes more pronounced with worsening obstruction (after the pause). **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester. West Sussex: Wiley Blackwell.

Table 4-30: ACC/AHA Recommendations on Angiography and Invasive Hemodynamic Assessment:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Coronary angiography (CT or invasive) is recommended in patients with HCM who are: (i) symptomatic, or (ii) with evidence of myocardial ischemia, or (iii) who are at risk of coronary atherosclerosis before surgical myectomy.</i> | I | B |
| <i>In symptomatic patients with HCM and inconclusive non-invasive cardiac imaging, left and right heart catheterization may be considered to assess the severity of LVOTO and to measure LV filling pressures.</i> | IIb | C |

▪ **Genetic testing for diagnosis; screening of first-degree relatives:**

- Genetic testing identifies definite pathogenic mutations in only 40-60% of HCM cases. Therefore, a positive test definitely establishes the HCM genotype, but a negative test is unhelpful.
- In about half of cases, HCM is inherited as an autosomal dominant. Apparently sporadic cases can have a monogenic cause, either because of incomplete penetrance **or** due to de novo variants that were not carried by the parents **or**, less commonly, due to autosomal recessive inheritance.
- Genetic testing of an index patient is indicated for family screening purposes. If the patient tests positive for a definite mutation, first-degree family members should be screened for that mutation.

The absence of this mutation in a family member excludes the risk of HCM occurrence and is reassuring.

A positive genotype with a negative phenotype in a family member indicates a considerable risk of developing HCM; routine ECG and echo follow-up is performed throughout life.

- Short of genetic testing, first-degree relatives of HCM patients should undergo ECG and echocardiograms every **1-2 years** starting in early adolescence and until the age of 21. Afterwards, they need to be screened every 5 years for the late development of HCM (more frequent interval in case of athletic activity or family history of SCD).

| Table 4-31: Screening with ECG and 2D Echocardiography in Asymptomatic Family Members ⁽¹⁾: | | |
|--|--------------------------------|-------------------------|
| Age of First-Degree Relative | Initiation of Screening | Repeat ECG, Echo |
| Children and adolescents from genotype-positive | | Every 1-2 y |

(1) Includes all asymptomatic, phenotype-negative first-degree relatives deemed to be at-risk for developing HCM based on family history or genotype status and may sometimes include more distant relatives based on clinical judgment. Screening interval may be modified (eg, at onset of new symptoms or in families with a malignant clinical course or late-onset HCM).

| | | |
|---|---|-------------|
| families, and families with early onset disease | At the time HCM is diagnosed in another family member | |
| All other children and adolescents | | Every 2-3 y |
| Adults | | Every 3-5 y |

| Table 4-32: ESC Recommendations on genetic testing in patients with HCM: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Genetic testing in probands: | | |
| <i>Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.</i> | I | B |
| <i>In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.</i> | I | B |
| <i>Genetic testing in patients with a borderline ⁽¹⁾ diagnosis of HCM should be performed only after detailed assessment by specialist teams.</i> | IIa | C |
| <i>Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.</i> | IIa | C |
| Genetic and clinical testing of adult relatives: | | |
| <i>Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.</i> | I | B |

(1) **Borderline:** left ventricular wall thickness 12-13 mm in adults; LVH in presence of hypertension, athletic training, valve disease.

| | | |
|---|------------|----------|
| <i>Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband.</i> | I | C |
| <i>First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.</i> | IIa | B |
| <i>When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2-5 years (or 6-12 monthly if non-diagnostic abnormalities are present).</i> | IIa | C |
| Genetic and clinical screening in children: | | |
| <i>The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing when they are aged ≥ 10 years and this should be carried out in accordance with international guidelines for genetic testing in children.</i> | IIa | C |
| <i>In first-degree child relatives aged ≥ 10 years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1-2 years between 10 and 20 years of age, and then every 2-5 years thereafter.</i> | IIa | C |
| <i>If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or be substituted for genetic</i> | IIb | C |

| | | |
|---|------------|----------|
| <i>evaluation after counselling by experienced physicians and when it is agreed to be in the best interests of the child.</i> | | |
| <i>When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives before the age of 10 years may be considered.</i> | IIb | C |

Differential diagnosis:

▪ Differential diagnosis of severe LVH:

- Severe LVH (septal thickness > 15 mm, sometimes > 20 mm) may be seen in **hypertension** or **AS** and may be asymmetric and/or obstructive.
- In older patients, elongation of the aorta changes the angle of the aortic–septal junction and leads to a **sigmoid septum**. A sigmoid septum exaggerates the degree of asymmetric septal hypertrophy and may lead to LVOT obstruction.
- A severe increase in septal thickness may also be seen with **infiltrative disorders such as amyloidosis**; in this case, thickening of the valve leaflets and the interatrial septum is often seen, along with a pericardial effusion. Cardiac MRI and endomyocardial biopsy may distinguish hypertrophic from amyloid cardiomyopathy.

▪ Differential diagnosis of LVOT obstruction:

- **Patients with hypertension** and generalized or asymmetric LVH may develop intracavitary LV obstruction, particularly in case of hypovolemia. LVOT obstruction and a true LVOT gradient, sometimes exceeding 100 mmHg, may be seen, with occasional SAM of the mitral valve. This is called “hypertensive hypertrophic cardiomyopathy” or “hypertensive obstructive cardiomyopathy,” and unlike HOCM, is not associated with myofibrillar disarray.

Clinical features favouring hypertension only:

- Normal 12 lead ECG or isolated increased voltage without repolarisation abnormality.

- Regression of LVH over 6-12 months after tight systolic blood pressure control (< 130 mmHg).

Clinical features favouring hypertrophic cardiomyopathy:

- Family history of HCM.
 - RV hypertrophy.
 - LGE at the RV insertion points or localized to segments of maximum LV thickening on CMR.
 - Maximum LV wall thickness ≥ 15 mm (Caucasian); ≥ 20 mm (black).
 - Severe diastolic dysfunction.
 - Marked repolarisation abnormalities, conduction disease or Q-waves on 12 lead ECG.
- **Subaortic obstruction** and severe asymmetric septal hypertrophy may be seen in ~10% of patients with severe AS and is unmasked after aortic valve replacement (septal thickness up to 22 mm). Doppler flow acceleration develops postoperatively and is attributed to LVOT obstruction and SAM.
This obstruction is associated with postoperative hypotension, increased morbidity and mortality, and long-term persistence of a gradient in some patients. It is mainly treated medically (β -blockers, avoidance of inotropes, fluid resuscitation); a limited pre-emptive myectomy has been selectively used in patients with septal bulge, with good results.
 - Another form of subvalvular obstruction is **subvalvular aortic stenosis** that results from a discrete fibrous membrane or fibromuscular thickening within the outflow tract, just below the aortic valve.
It leads to a fixed obstruction, the characteristics of dynamic LVOT obstruction being absent: no dagger-shaped LV pressure, no spike-and-dome aortic pressure, and no Brockenbrough phenomenon. As opposed to HOCM, the gradient does not worsen with maneuvers such as Valsalva.
 - **Patients receiving dobutamine:** LVOT obstruction is frequently seen regardless of the presence of LVH and does not signify HOCM per se, as the obstruction may not be reproduced during exercise in most of these patients. It may also be seen in hospitalized patients with severe hypovolemia or sepsis and an empty, hypercontractile LV cavity, even if LVH is mild.
 - A pattern of LVOT obstruction and mitral SAM may also be seen in **patients with apical dyskinesia and hypercontractile LV base**, as in large anteroapical infarction or takotsubo cardiomyopathy.

N.B: Difference between HOCM and AS:

| Table 4-33: Difference between HOCM and AS: | | |
|---|--|---|
| | HOCM ⁽¹⁾ | Aortic Stenosis |
| Quality | <i>Harsh, crescendo-decrescendo mid systolic murmur</i> | <i>Harsh, crescendo-decrescendo mid-systolic murmur</i> |
| Location | <i>Lower left sternal border</i> | <i>Right upper sternal border</i> |
| Radiation | <i>Apex/axilla, not carotids</i> | <i>Carotids</i> |
| Carotid pulse | <i>Brisk, double-peaked (bisferens)</i> | <i>Slow, small amplitude</i> |
| Dynamic with maneuvers (Valsalva, Handgrip, standing) | <i>++++</i> | <i>+ (changes are not usually audible)</i> |
| Apical impulse | <i>Enlarged, triple ripple (systolic ejection, systolic obstruction and S₄)</i> | <i>Enlarged, Single impulse</i> |

(1) MR murmur (SAM) may also be heard with HOCM: blowing, holosystolic murmur at the apex while HOCM murmur is best heard at the Lower left sternal border. This MR murmur is also worse with valsalva. The two murmurs are heard at two different locations and are both dynamic.

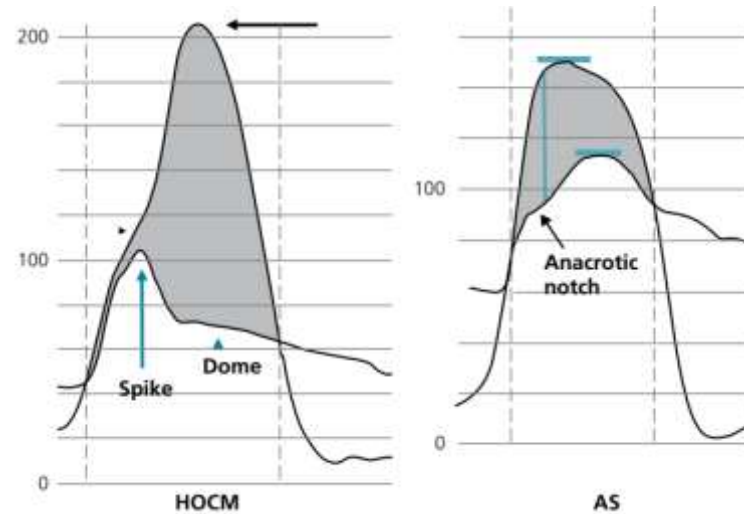


Figure 4-23: LV–aortic tracings in HOCM vs. AS. In HOCM, the aortic pressure peaks early while the LV pressure and the gradient peak late, after a bend (*arrowhead*). In AS, the LV pressure peaks early while the aortic pressure peaks late, after an anacrotic notch. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

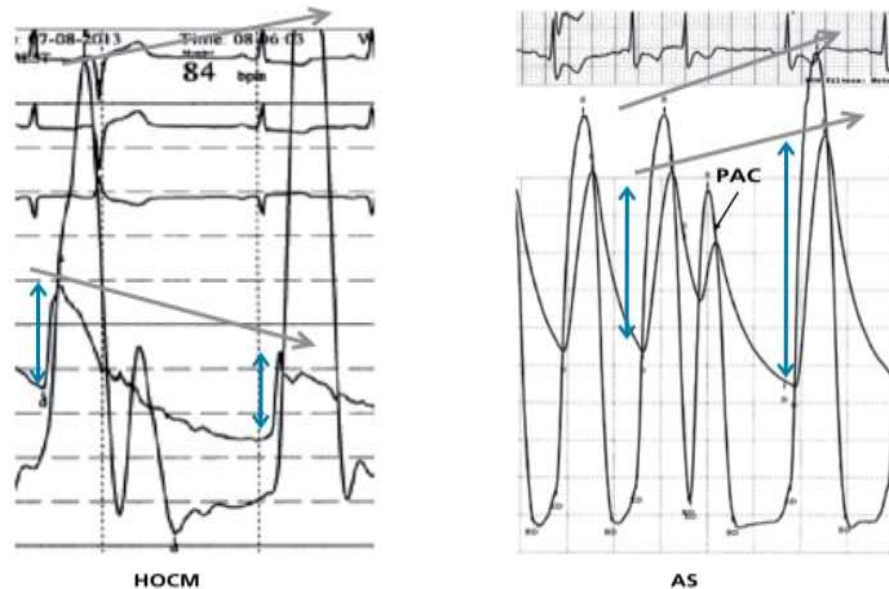


Figure 4-24: Brockenbrough phenomenon after a premature beat in HOCM. Note the increased pressure gradient but reduced aortic pulse pressure (*double arrows*) after a pause in HOCM, vs. the increased pressure gradient but also increased aortic systolic and pulse pressure in AS. The *arrows* indicate the change in LV pressure vs. aortic pressure. The pressure gradient increases much more markedly with HOCM than with AS after this pause. Also, because of the increased obstruction, *the spike-and-dome morphology becomes more apparent after a pause*. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Treatment:

I. HCM with LVOT obstruction:

- **General measures:**
 - All patients with LVOTO should avoid dehydration and excess alcohol consumption, and weight loss should be encouraged.

- Diuretics and vasodilators, including nitrates and phosphodiesterase type 5 inhibitors, worsen LVOT obstruction by reducing preload and afterload, respectively, and thus should be avoided. A small diuretic dose may be carefully used in HOCM patients with persistent congestive symptom.
- **Pharmacological treatment:**
 - In symptomatic patients with LVOTO, the pharmacologic therapy is targeted at the dynamic LV obstruction to improve functional capacity and reduce symptoms (these drugs do not affect SCD). The success of a given drug is determined by the symptom response, not the measured gradient.
 - In symptomatic patients without LVOTO focuses on management of arrhythmia, reduction of LV filling pressures, and treatment of angina.
 - Medical therapy consists of agents reducing inotropism and chronotropism: **β-blockers or non-DHP CCBs**. By reducing inotropism and the LV ejection speed, they reduce the mitral valve drag. By reducing the heart rate, they increase preload and diastolic filling time, and reduce functional ischemia. The combination of a β-blocker and a CCB is best avoided. While heart rate reduction is useful, severe bradycardia (< 50 bpm) or long pauses are harmful as they lead to increased myocardial contractility and thus increased gradient (similar to Brockenbrough phenomenon).
 - If beta-blockers alone are ineffective, **disopyramide** (class Ia antiarrhythmic drug with potent negative inotropic effect and mild vasoconstrictive effect) titrated up to a maximum tolerated dose (usually 400–600 mg/day), could be considered as a second-line, add-on therapy.
 - **Mavacamten** (A novel negative inotrope, myosin inhibitor) may be added to β-blocker or CCB, with a dramatic improvement of symptoms and LVOT gradient (EXPLORER-HCM trial).
 - **Acute therapy of acute HF or shock:**
 - Patients with HOCM who develop pulmonary edema are acutely treated with β-blockers ⁽¹⁾. Diuretics may worsen LVOT obstruction and thus, paradoxically, worsen pulmonary edema.

(1) Mitral stenosis and HOCM are the only two conditions wherein acute pulmonary edema is treated with β-blockers.

- Patients with HOCM who develop hypotension are treated with intravenous hydration. If pulmonary edema is also present, α -agonists may be used, as they increase afterload and thus reduce LVOT obstruction. Positive inotropes should be avoided.

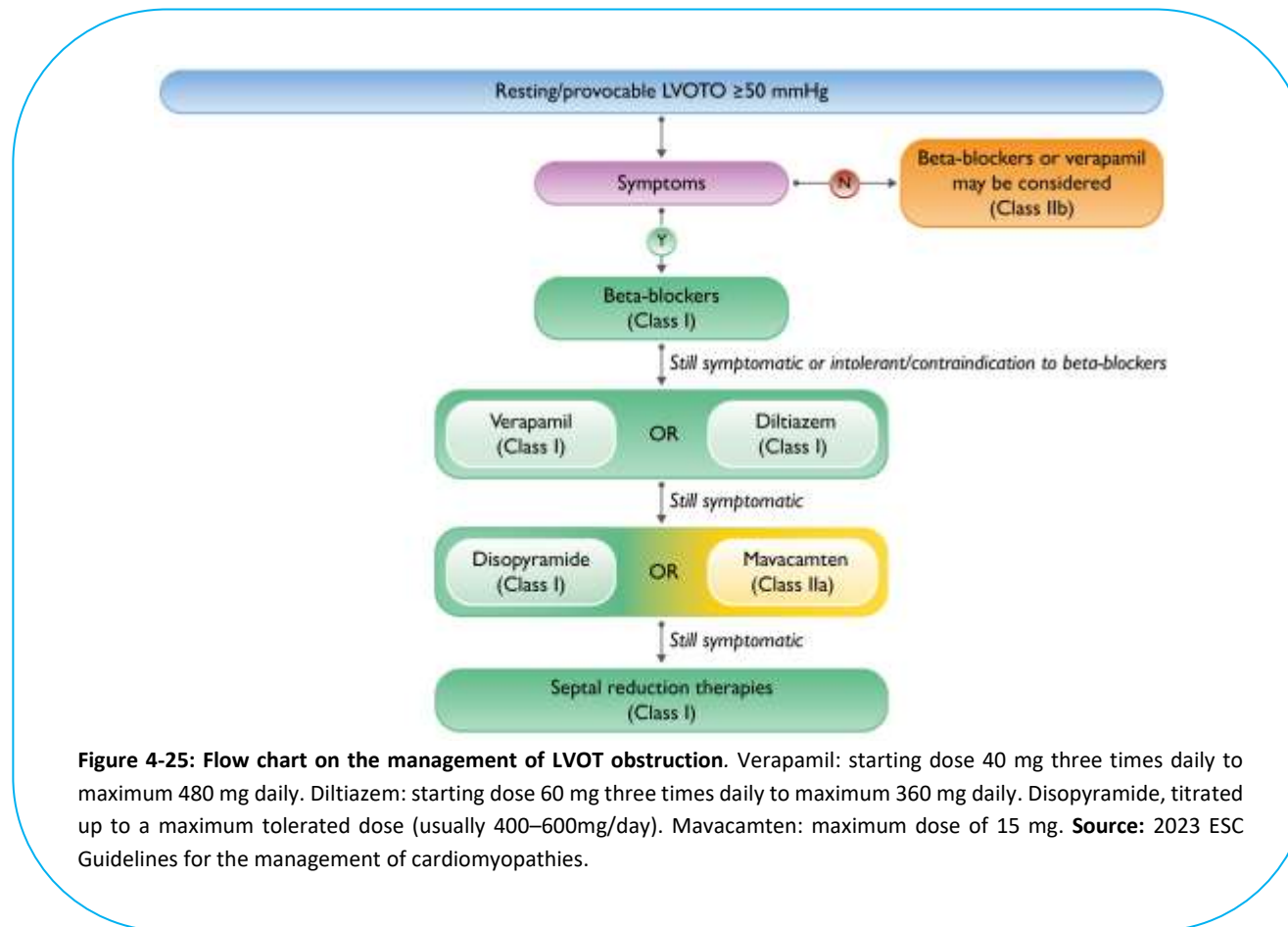


Table 4-34: ESC Recommendations for Pharmacologic Management of Patients with Obstructive HCM:

| Recommendation | Class | Level |
|---|--------------|--------------|
| General measures: | | |
| <i>Avoidance of digoxin and arterial and venous dilators, including nitrates and phosphodiesterase inhibitors, should be considered, if possible, in patients with resting or provokable LVOTO.</i> | Ila | C |
| Pharmacological treatment: | | |
| <i>Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provokedc LVOTO.</i> | I | B |
| <i>Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provokedc LVOTO who are intolerant or have contraindications to beta-blockers.</i> | I | B |
| <i>Disopyramide, ⁽¹⁾ titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provokedc LVOTO.</i> | I | B |
| <i>Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provokedc LVOTO.</i> | Ila | A |
| <i>Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in</i> | Ila | B |

(1) QTc interval should be monitored during up-titration of disopyramide and the dose reduced if it exceeds 500 ms. Dose-limiting anticholinergic side effects include dry eyes and mouth, urinary hesitancy or retention, and constipation.

| | | |
|--|------------|----------|
| <i>symptomatic adult patients with resting or provoked ⁽¹⁾ LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/ diltiazem, or disopyramide.</i> | | |
| <i>Oral or i.v. beta-blockers and vasoconstrictors should be considered in patients with severe provokable LVOTO presenting with hypotension and acute pulmonary oedema who do not respond to fluid administration.</i> | IIa | C |
| <i>Disopyramide, titrated to maximum tolerated dose, may be considered as monotherapy in patients who are intolerant to or have contraindications to beta-blockers and verapamil/diltiazem to improve symptoms in patients with resting or provoked LVOTO.</i> | IIb | C |
| <i>Beta-blockers or verapamil may be considered in selected cases in asymptomatic patients with resting or provoked LVOTO to reduce LV pressures.</i> | IIb | C |
| <i>The cautious use of low-dose diuretics may be considered in symptomatic LVOTO to improve exertional dyspnoea.</i> | IIb | C |

(1) Provocation with Valsalva manoeuvre, upright exercise, or oral nitrates if unable to exercise.

- **Invasive septal reduction:**

- Septal reduction strikingly improves symptoms and the long-term risk of HF-related death. Myectomy may also reduce the risk of SCD.
- Septal reduction to reduce LVOTO should be considered in patients with a LVOTO gradient ≥ 50 mmHg, severe symptoms (NYHA functional class III–IV), and/or exertional or unexplained recurrent syncope in spite of maximally tolerated drug therapy. Septal reduction may also be considered in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked gradient of ≥ 50 mmHg (exercise or Valsalva) and moderate-to-severe systolic anterior motion-related mitral regurgitation, AF, or moderate-to-severe left atrial dilatation in expert centres with low procedural complication rates.

- **There are two modalities of septal reduction:**

- **Surgical myectomy:** Myectomy consists of resecting the septal bulge through the aortic valve and has a low operative mortality ($< 1\%$). It is associated with a total abolition of gradient and symptom resolution in $> 90\%$ of patients, with normalization of long-term survival. In addition, it appears to be associated with a reduction of the risk of ventricular arrhythmia (reduction of yearly ICD discharges).

In patients with intrinsic/primary mitral valve disease or marked mitral leaflet elongation and/or moderate-to-severe mitral regurgitation, septal myectomy can be combined with mitral valve surgery. In patients with AF, concomitant ablation using the Cox–Maze procedure can also be performed. In infants and very young children, the modified Konno procedure may be an alternative to myectomy when the aortic annulus is too small.

- **Alcohol septal ablation:** Alcohol septal ablation is a percutaneous coronary procedure that consists of wiring the first or large septal branch that supplies the basal septum and injecting it with alcohol through a balloon catheter. This leads to infarction of the basal septum. The operative mortality is $\sim 1\%$, and the symptomatic improvement is similar to that of myectomy. An acute response with a striking gradient reduction (due to stunning of the myocardium) is followed by a gradient rise to about 50% of the pre-procedural level the next day(s), then a progressive septal remodeling and a great reduction of the gradient over 3 months. MR also improves with septal ablation.

Alcohol ablation is associated with an early risk of VT/VF (as with any MI).

Limitations:

- ☞ Alcohol ablation value is more limited in patients with one, and particularly two, of the following: severe septal hypertrophy (≥ 30 mm), LVOT gradient > 100 mmHg, age < 65 years.
- ☞ It is also limited in patients with mitral valve abnormalities contributing to LVOT obstruction.

○ **Complications:**

- AV block: 2% in surgical myectomy and 7–20% in alcoholic septal ablation.
- Bundle branch block (LBBB in septal myectomy and RBBB in alcohol septal ablation),
- Ventricular septal defect: higher in patients with mild hypertrophy (≤ 16 mm) at the point of the mitral leaflet–septal contact.
- Residual LVOT gradients (more in alcoholic septal ablation).

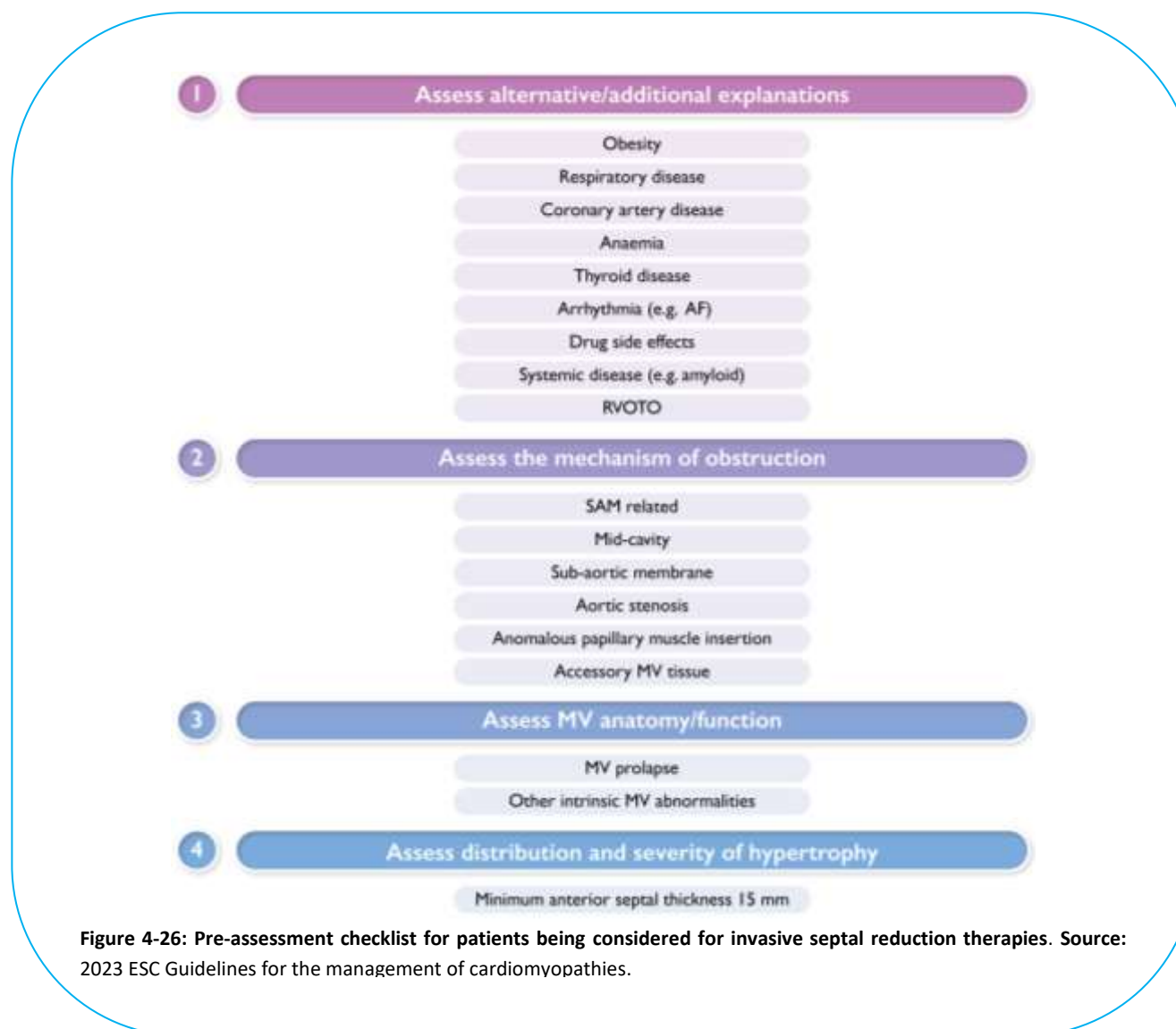


Figure 4-26: Pre-assessment checklist for patients being considered for invasive septal reduction therapies. Source: 2023 ESC Guidelines for the management of cardiomyopathies.

| Table 4-35: ESC Recommendations on septal reduction therapy: | |
|--|-------------|
| Recommendation | Class Level |

| | | |
|--|------------|----------|
| <i>It is recommended that SRT be performed by experienced operators working as part of a multidisciplinary team expert in the management of HCM.</i> | I | C |
| <i>SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥ 50 mmHg who are in NYHA/Ross functional class III–IV, despite maximum tolerated medical therapy.</i> | I | B |
| <i>Septal myectomy, rather than ASA, is recommended in children with an indication for SRT, as well as in adult patients with an indication for SRT and other lesions requiring surgical intervention (e.g. mitral valve abnormalities).</i> | I | C |
| <i>SRT should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥ 50 mmHg despite optimal medical therapy.</i> | IIa | C |
| <i>Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient ≥ 50 mmHg and moderate-to-severe mitral regurgitation that cannot be corrected by SRT alone.</i> | IIa | C |
| <i>Mitral valve repair should be considered in patients with a resting or maximum provoked LVOTO gradient ≥ 50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy.</i> | IIa | C |
| <i>SRT may be considered in expert centres with demonstrable low procedural complication rates in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked (exercise or Valsalva) gradient of ≥ 50 mmHg and:</i> | IIb | C |

| | | |
|--|------------|----------|
| - moderate-to-severe SAM-related mitral regurgitation; or - AF; or - moderate-to-severe left atrial dilatation. | | |
| Mitral valve replacement may be considered in patients with a resting or maximum provoked LVOTO gradient ≥ 50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy. | IIb | C |
| Surgical AF ablation and/or left atrial appendage occlusion procedures during septal myectomy may be considered in patients with HCM and symptomatic AF. | IIb | C |

- **AV sequential ventricular pacing:**

- Ventricular apical pacing leads to a delayed and less effective contraction of the basal septum, which reduces the LVOT narrowing.
- Despite a real reduction of gradient in most patients, the effect of pacing on symptoms is controversial: 40-60% of patients show symptomatic improvement with DDD pacing, yet the same number of patients show symptomatic improvement with atrial pacing (placebo). This implies that most of the symptomatic benefit from pacing is a placebo effect.
- DDD pacing with ventricular capture is recommended in patients who otherwise have an indication for pacing **or** patients who are not candidates for septal reduction **or** symptomatic patients > 65 years undergoing ICD placement for SCD prevention (consider dual chamber instead of single-chamber ICD).
- Severe bradycardia (< 50 bpm) is less likely to be tolerated in HOCM than in normal individuals, as it leads to increased contractility and increased gradient.
- In symptomatic patients whose rate is < 50 bpm or even 50-60 bpm, and who cannot tolerate β -blockade because of rate, pacing followed by aggressive β -blockade may be used, especially if an ICD, which has pacing capacity, is required for sudden death prevention. However, septal ablation may be a better alternative for the latter patients.

Table 4-36: ESC Recommendations for indications for cardiac pacing in patients with obstruction:

| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| <i>Sequential AV pacing, with optimal AV interval to reduce the LV outflow tract gradient or to facilitate medical treatment with beta-blockers and/or verapamil, may be considered in selected patients with resting or provokable LVOTO ≥ 50 mmHg, sinus rhythm, and drug-refractory symptoms, who have contraindications for ASA or septal myectomy or are at high risk of developing heart block following ASA or septal myectomy.</i> | IIb | C |
| <i>In patients with resting or provokable LVOTO ≥ 50 mmHg, sinus rhythm, and drug-refractory symptoms, in whom there is an indication for an ICD, a dual-chamber ICD (instead of a single-lead device) may be considered, to reduce the LV outflow tract gradient or to facilitate medical treatment with beta-blockers and/or verapamil.</i> | IIb | C |

II. HCM without LVOT obstruction:

Table 4-37: ACC and ESC Recommendations on Management of Patients with Non-obstructive HCM with Preserved EF:

| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| Chest Pain: | | |
| <i>Beta-blockers and calcium antagonists (verapamil or diltiazem) should be considered to improve symptoms in patients with angina-like chest pain even in the absence of LVOTO or obstructive CAD.</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>Oral nitrates may be considered to improve symptoms in patients with angina-like chest pain, even in the absence of obstructive CAD, if there is no LVOTO.</i> | IIb | C |
| <i>Ranolazine may be considered to improve symptoms in patients with angina-like chest pain even in the absence of LVOTO or obstructive CAD.</i> | IIb | C |
| Atrial fibrillation: | | |
| <i>In patients with HCM and clinical AF, anticoagulation is recommended with NOACs as first-line option and VKA as second-line option, independent of CHA₂DS₂-VASc score.</i> | I | B |
| <i>In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of > 24 hours' duration for a given episode, anticoagulation is recommended, independent of CHA₂DS₂-VASc score.</i> | I | C |
| <i>In patients with HCM and subclinical AF detected by internal or external device or monitor, of > 5 minutes' but < 24 hours' duration for a given episode, anticoagulation can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk.</i> | IIa | B |
| <i>In patients with AF in whom rate control strategy is planned, either beta-blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions.</i> | I | C |
| <i>In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>In patients with HCM and symptomatic AF, as part of a AF rhythm control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference.</i> | Ila | B |
| <i>In patients with HCM and AF who require surgical myectomy, concomitant surgical AF ablation procedure can be beneficial for AF rhythm control.</i> | Ila | B |

III. **HCM with Advanced HF:**

- As EF often overestimates myocardial systolic function in patients with HCM, guideline-directed medical therapy for HFrEF is initiated for EF < 50% (as opposed to < 40% in other heart failure populations) and otherwise is generally based on the Heart Failure Guidelines.
- CRT might be considered in individual symptomatic patients with LV impairment (LVEF < 50%) that meet current ESC ECG criteria (LBBB, QRS 130–149 ms), or in patients with HCM and impaired systolic function who require permanent ventricular pacing.
- Regardless of LVEF, if patients experience recurrent ventricular arrhythmias or severe (NYHA class III to class IV) symptoms despite optimization of medical therapy and SRT is not an option, heart transplant evaluation is warranted, and CPET plays a role in risk stratification.
- For patients with NYHA class III to class IV symptoms, an LVAD is sometimes used.

| Table 4-38: AHA/ACC Recommendations on Management of Patients with HCM With Advanced HF: | | |
|--|---------------------|---------------------|
| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
| <i>In patients with HCM who develop systolic dysfunction with an LVEF < 50%, guideline directed therapy for HFrEF is recommended.</i> | I | C |

| | | |
|--|------------|----------|
| <i>In patients with HCM and systolic dysfunction, diagnostic testing to assess for concomitant causes of systolic dysfunction (such as CAD) is recommended.</i> | I | C |
| <i>In patients with non-obstructive HCM and advanced HF (NYHA III-IV despite guideline-directed therapy), CPET should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support.</i> | I | B |
| <i>In patients with non-obstructive HCM and advanced HF (NYHA III-IV despite guideline-directed therapy) or with life threatening ventricular arrhythmias refractory to maximal guideline-directed therapy, assessment for heart transplantation in accordance with current listing criteria is recommended.</i> | I | B |
| <i>For patients with HCM who develop systolic dysfunction (LVEF < 50%), it is reasonable to discontinue previously indicated negative inotropic agents (specifically, verapamil, diltiazem, or disopyramide).</i> | IIa | C |
| <i>In patients with nonobstructive HCM and advanced HF (NYHA III-IV despite GDMT) who are candidates for heart transplantation, continuous-flow LVAD therapy is reasonable as a bridge to heart transplantation.</i> | IIa | B |
| <i>In patients with HCM and LVEF < 50%, ICD placement can be beneficial.</i> | IIa | C |
| <i>In patients with HCM and LVEF < 50%, NYHA II-IV symptoms despite guideline-directed therapy, and LBBB, CRT can be beneficial to improve symptoms.</i> | IIa | C |

IV. Sudden cardiac death risk assessment and ICD therapy:

- Annual incidence for CV death in adult patients with HCM is 1–2%, with SCD, heart failure, and thrombo-embolism being the main causes of death. The most commonly recorded fatal arrhythmic event is spontaneous VF, but asystole, AV block, are described. In children with HCM, SCD rates is > 50% higher than reported in adult HCM populations.
- It is recommended to use **HCM Risk-SCD** tool as the first step in sudden death prevention in patients aged 16 years or more, and to use of **HCM Risk-Kids** tool for children and adolescents < 16 years. These models should not be used in elite athletes or in individuals with metabolic/infiltrative diseases (e.g. Anderson–Fabry disease) and syndromes (e.g. Noonan syndrome). The models have not been validated before and after myectomy.
- There is no evidence supporting a significant role of drugs to prevent SCD. Amiodarone may reduce VA but with conflicting results regarding SCD prevention. Disopyramide and beta-blockers are efficient to control symptoms and LVOT obstruction, not SCD. Similarly, surgical myectomy or alcohol ablation are not recommended with the aim to reduce risk of SCD in patients with LVOT obstruction.

Table 4-39: Major clinical features associated with an increased risk of sudden cardiac death:

Established Clinical Risk Factors for HCM-SCD risk score:

| | |
|--|--|
| Age | <ul style="list-style-type: none"> ○ <i>There is an increased risk of SCD in younger patients.</i> ○ <i>Sudden cardiac death is very rare below the age of 6 years.</i> |
| Unexplained syncope | <p><i>Unexplained syncope is a syncope that occurs at rest, during sitting, lying, light activity, or during peak exercise.</i></p> <p><i>Episodes within 6 months of evaluation may be more predictive of SCD (associated with a 5-fold increase in SCD).</i></p> |
| Family history of sudden death from HCM | <ul style="list-style-type: none"> ○ <i>Family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.</i> ○ <i>Family history of SCD does not appear to be an independent risk factor for SCD in childhood HCM.</i> |

| | |
|---|---|
| NSVT | <ul style="list-style-type: none"> ○ NSVT (defined as ≥ 3 consecutive ventricular beats at ≥ 120 b.p.m. lasting < 30s) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD. ○ There is no evidence that the frequency, duration, or rate of NSVT influences the risk of SCD. ○ NSVT occurring during or immediately following exercise is very rare, but may be associated with a high risk of SCD. |
| Maximum LV wall thickness | Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥ 30 mm. |
| Left atrial diameter | Several studies have reported a positive association between LA size and SCD. There are no data on the association between SCD and LA area or volume. |
| LV outflow tract obstruction | A number of studies have reported a significant association between LVOTO and SCD risk. |
| Other recently proposed risk factors of SCD in HCM ⁽¹⁾: | |
| HCM with LV systolic dysfunction | <p>Systolic dysfunction with EF $< 50\%$ by echocardiography or CMR imaging.</p> <p>Studies consistently show an increased rate of SCD events in patients with LV systolic dysfunction. However, the independent and additional value of LVSD compared with current risk stratification tools has not been investigated.</p> |
| LV apical aneurysm | <ul style="list-style-type: none"> ○ Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the left ventricle and are often associated with a mid-cavity gradient. ○ 2020 AHA/ACC HCM guidelines consider it as a major independent SCD risk factor. However, ESC guidelines stated that ICD decisions should not solely be based on the presence of an LV apical aneurysm. |

(1) ESC guidelines recommend to first estimate SCD risk using the HCM-SCD Risk calculators. For patients who are in the low to intermediate risk category, the presence of these factors may be used in shared decision-making with patients about prophylactic ICD implantation, acknowledging the lack of robust data on the impact of scar quantification on the personalized risk estimates generated by the HCM-SCD Risk calculators.

**Extensive LGE on
CMR imaging**

Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising $\geq 15\%$ of LV mass (extent of LGE conferring risk has not been established in children).

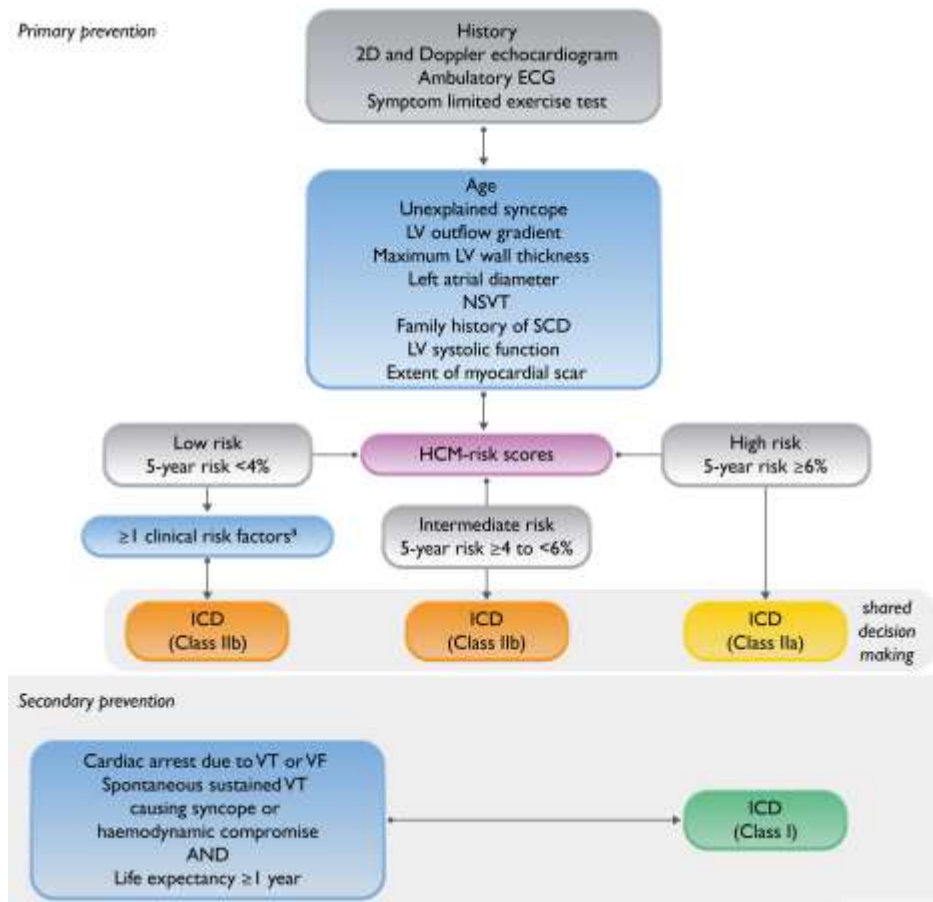


Figure 4-27: Flow chart for implantation of an ICD in patients with HCM. * Clinical risk factors: extensive LGE ($> 15\%$) on CMR; LVEF $< 50\%$. **Source:** 2023 ESC Guidelines for the management of cardiomyopathies.

Table 4-40: ESC Recommendations for management of VA and SCD in HCM:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Diagnostic evaluation and general recommendations: | | |
| <i>CMR with LGE is recommended in HCM patients for diagnostic work-up.</i> | I | B |
| <i>Genetic counselling and testing are recommended in HCM patients.</i> | I | B |
| <i>Participation in high-intensity exercise may be considered for asymptomatic adult HCM patients without risk markers.</i> | IIb | C |
| Risk stratification and primary prevention of SCD: | | |
| <i>The HCM Risk-SCD calculator is recommended as a method of estimating risk of sudden death at 5 years in patients aged ≥ 16 years for primary prevention.</i> | I | B |
| <i>Validated paediatric-specific risk prediction models (e.g. HCM Risk-Kids) are recommended as a method of estimating risk of sudden death at 5 years in patients aged < 16 years for primary prevention.</i> | I | B |
| <i>It is recommended that the 5-year risk of SCD is assessed at first evaluation and at 1-3-year intervals, or when there is a change in clinical status.</i> | I | C |
| <i>ICD implantation should be considered in patients with an estimated 5-year risk of SD $\geq 6\%$. (using HCM Risk-SCD for adults, HCM Risk-Kids for children 1-16 years)</i> | IIa | B |
| <i>ICD implantation should be considered in HCM patients aged 16 years or more with an intermediate 5-year risk of SCD (≥ 4 to $< 6\%$) ⁽¹⁾ and with (A) significant LGE at CMR (usually $\geq 15\%$ of LV mass); or (B) LVEF $< 50\%$; or (C) LV apical aneurysm; or (D) abnormal blood pressure response during exercise test ⁽²⁾; or (E) presence of sarcomeric pathogenic mutation.</i> | IIa | B |

(1) Based on the HCM Risk-SCD: <https://doc2do.com/hcm/webHCM.html>

(2) Defined as a failure to increase systolic pressure by at least 20 mmHg from rest to peak exercise, or a fall of > 20 mmHg from peak pressure.

| | | |
|---|------------|----------|
| <i>ICD implantation may be considered in HCM patients aged 16 years or more with an estimated 5-year risk of SCD of ≥ 4 to $< 6\%$.</i> | IIb | B |
| <i>ICD implantation may be considered in HCM patients aged 16 years or more with a low estimated 5-year risk of SCD ($< 4\%$) and with (A) significant LGE at CMR (usually $\geq 15\%$ of LV mass); or (B) LVEF $< 50\%$; or (C) LV apical aneurysm.</i> | IIb | B |
| Secondary prevention of SCD and treatment of VAs: | | |
| <i>ICD implantation:</i> | | |
| <i>- is recommended in HCM patients with haemodynamically not-tolerated VT or VF.</i> | I | B |
| <i>- should be considered in patients with HCM presenting with haemodynamically tolerated SMVT.</i> | IIa | C |
| <i>In patients with HCM and recurrent, symptomatic VA, or recurrent ICD therapy, AAD treatment should be considered.</i> | IIa | C |
| <i>Catheter ablation in specialized centres may be considered in selected patients with HCM and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AAD are ineffective, contraindicated, or not tolerated.</i> | IIb | C |
| Management of relatives of a patient with HCM: | | |
| <i>In a first-degree relative of a patient with HCM, ECG and echocardiogram are recommended.</i> | I | C |

V. Treatment of patients with storage disorders:

- **For patients with Anderson-Fabry disease:**
 - Enzyme replacement therapy with agalsidase- α and agalsidase- β .
 - Oral chaperone: migalastat.
- **For patients with Pompe disease (glycogen storage disease type II):**
 - Enzyme replacement therapy with recombinant human α -glucosidase.
- **For patients with Danon disease:** no specific therapy. Close follow-up is recommended due to the malignant nature of the disease, including low threshold for ICD implantation and early listing for heart transplantation in appropriate candidates.

Follow-up:

Table 4-41: ESC Recommendations on follow up of patients with HCM:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>A clinical evaluation, including 12-lead ECG and TTE, is recommended every 1-2 years in clinically stable patients or whenever there is a change in symptoms.</i> | I | C |
| <i>48-Hour ambulatory ECG is recommended every 1-2 years in clinically stable patients, every 6-12 months in patients in sinus rhythm with LA dimension 45 mm, and whenever patients complain of new palpitations.</i> | I | C |
| <i>CMR may be considered every 5 years in clinically stable patients, or every 2-3 years in patients with progressive disease.</i> | IIb | C |
| <i>Symptom-limited exercise testing should be considered every 2-3 years in clinically stable patients, or every year in patients with progressive symptoms.</i> | IIa | C |
| <i>Cardiopulmonary exercise testing (when available) may be considered every 2-3 years in clinically stable patients, or yearly in patients with progressive symptoms.</i> | IIb | C |

Exercise recommendations:

Table 4-42: AHA/ACC Recommendations on lifestyle considerations in patients with HCM:

| Recommendation | Class | Level |
|---|--------------|--------------|
| Traditionally, it has been thought that exercise increases LV obstruction and LV ischemia, exposing the athlete to an immediate risk of arrhythmia, and a long-term risk of progressive fibrosis, hence the restriction of physical activity to low-intensity sports. Yet, recent data suggest that moderate or even high-intensity | | |

| | | |
|---|------------|----------|
| intensity sports may be safe and associated with improved LV compliance. Also, higher conditioning improves vagal tone and potentially arrhythmias (including VT). | | |
| <i>High-intensity exercise and competitive sport should be considered in genotype-positive/phenotype-negative individuals who seek to do so.</i> | IIa | C |
| <i>High-intensity exercise and competitive sport may be considered in asymptomatic low-risk individuals with morphologically mild hypertrophic cardiomyopathy in the absence of resting or inducible left ventricular outflow obstruction and exercise-induced complex ventricular arrhythmias.</i> | IIb | B |
| <i>High-intensity exercise, including competitive sport, is not recommended in high-risk individuals and in individuals with left ventricular outflow tract obstruction and exercise-induced complex ventricular arrhythmias.</i> | III | C |

Important trials in Specific Cardiomyopathies:

| Table 4-43: Clinical trials of specific cardiomyopathies: | |
|---|--|
| Trial (date) | Summary |
| Amyloidosis: | |
| ATTR-ACT (2018) | <p>Aim: To evaluate tafamidis compared with placebo among patients with transthyretin amyloid cardiomyopathy.</p> <p>Study: 441 patients with transthyretin amyloid cardiomyopathy were randomly assigned in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. Tafamidis was associated with reductions in all-cause mortality and CV hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo.</p> |
| Hypertrophic cardiomyopathy: | |
| TEMPO (2021) | <p>Aim: To investigate the effects of metoprolol on LVOT obstruction, symptoms, and exercise capacity in patients with HOCM.</p> <p>Study: 29 patients with HOCM and NYHA class II-IV were randomly assigned to receive metoprolol or placebo for 2 consecutive 2-week periods. The effect parameters were LVOT gradients, NYHA class, Canadian Cardiovascular Society (CCS) angina class, Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), and cardiopulmonary exercise testing. Metoprolol reduced LVOT obstruction at rest and during exercise, provided symptom relief, and improved quality of life in patients with HOCM. Maximum exercise capacity remained unchanged.</p> |
| EXPLORER-HCM (2020) | <p>Aim: To characterize the effect of mavacamten on LVOT gradient among patients with HOCM.</p> <p>Study: 251 patients HOCM (LVOT gradient ≥ 50 mmHg), LVEF $\geq 55\%$ and NYHA class II-III symptoms were randomized to mavacamten 5 mg daily versus placebo for 30 weeks. The primary outcome, ≥ 1.5 ml/kg/min increase in pVO₂ with ≥ 1 NYHA class improvement or ≥ 3.0 ml/kg/min increase in pVO₂ with no worsening of NYHA class at</p> |

| | |
|---------------------------|--|
| | <i>30 weeks. Mavacamten significantly improved measures of LV diastolic function and SAM. Improvement in LVOT obstruction, LAVI, and E/e' was associated with reduction in NT-pro-BNP.</i> |
| PIONEER-HCM (2019) | <p>Aim: <i>To evaluate mavacamten compared with placebo among patients with HOCM.</i></p> <p>Study: <i>21 symptomatic patients with HOCM were assigned to mavacamten (10 to 20 mg/d) without background medications, or to mavacamte (2 to 5 mg/d) with β-blockers allowed. The primary end point was change in postexercise LVOT gradient at 12 weeks. Mavacamten can reduce LVOT obstruction and improve exercise capacity and symptoms in patients with HOCM.</i></p> |
| VALOR-HCM (2023) | <p>Aim: <i>To examine the cumulative longer-term effect of mavacamten on the need for SRT through week 56.</i></p> <p>Study: <i>108 patients with obstructive HCM (NYHA class III/IV) referred for SRT were randomized to mavacamten (5 mg and titrated) or placebo. After 16 weeks, patients originally randomized to placebo were crossed over to 5 mg of mavacamten daily. The primary endpoint was decision to proceed with SRT or guideline eligible at week 16. Mavacamten for 16 weeks improved symptoms and significantly reduced eligibility for needing SRT among symptomatic patients with obstructive HCM, with sustained improvements in LVOT gradients and symptoms.</i></p> |
| REDWOOD-HCM (2023) | <p>Aim: <i>To evaluate the safety and efficacy of aficamten in patients with HOCM.</i></p> <p>Study: <i>41 Patients with HOCM and LVOT gradients ≥ 30 mm Hg at rest or ≥ 50 mm Hg with Valsalva were randomized 2:1 to receive aficamten or placebo. Aficamten resulted in substantial reductions in LVOT gradients with most patients experiencing improvement in biomarkers and symptoms.</i></p> |

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Section

II

Coronary Artery Diseases

TO THE POINT

Chronic Coronary Syndrome

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods. The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

Chronic coronary syndromes encompass an array of different presentations of ischaemic heart disease, including stable angina, heart failure owing to CAD, recent diagnosis of CAD or revascularization, long-standing CAD, angina with non-obstructive coronary arteries and asymptomatic CAD detected at screening.

Myocardial ischaemia in stable coronary artery disease are caused by a transient imbalance between blood supply and metabolic demand. **The consequences of ischaemia occur in a predictable temporal sequence that involves:**

- Increased H^+ and K^+ concentration in the venous blood draining the ischaemic territory.
- Signs of ventricular diastolic and systolic dysfunction with RWMA.
- Development of ST-T changes.
- Cardiac ischaemic pain (angina).

Main features of CCS:

- **Pathogenesis:** Stable anatomical atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation.
- **Natural history:** Stable symptomatic or asymptomatic phases which may be interrupted by ACS.

- **Mechanisms of myocardial ischaemia:** (i) Fixed or dynamic stenoses of epicardial coronary arteries; (ii) Microvascular dysfunction; (iii) Focal or diffuse epicardial coronary spasm. These mechanisms may overlap in the same patient and change over time.
- **Clinical presentations:**
 - **Effort induced angina caused by:** epicardial stenoses; microvascular dysfunction; vasoconstriction at the site of dynamic stenosis; or combination of all of that.
 - **Rest angina caused by:** Vasospasm (focal or diffuse); epicardial focal; epicardial diffuse; microvascular; combination of the above.
 - **Asymptomatic:**
 - because of lack of ischaemia and/or of LV dysfunction;
 - despite ischaemia and/or LV dysfunction.
 - **Ischaemic cardiomyopathy.**

Epidemiology:

The prevalence of angina in population-based studies increases with age in both sexes,

- From 5-7% in women aged 45-64 years **to** 10-12% in women aged 65-84 and
- From 4-7% in men aged 45-64 years **to** 12-14% in men aged 65-84.

Interestingly, angina is more prevalent in middle-aged women than in men, probably due to the higher prevalence of functional CAD -such as microvascular angina- in women, whereas the opposite is true in the elderly.

Prognosis:

Risk factors for the development of CAD: Hypertension, Hypercholesterolaemia, DM, Sedentary lifestyle, Obesity, Smoking, and a Family history.

An elevated resting heart rate is also indicative of a worse prognosis in those with suspected or proven CAD.

In general, the outcome is worse in patients with: Reduced LVEF and heart failure, a greater number of diseased vessels, more proximal locations of coronary stenoses, greater severity of lesions, more extensive ischaemia, more impaired functional capacity, older age, significant depression and more severe angina.

Causes of angina; pathophysiology of coronary flow:

A. Angina caused by fixed coronary obstruction:

Coronary blood flow constitutes *~5% of the total cardiac output* and may increase up to 5 times with exercise. Normally, the coronary microcirculatory resistance constitutes the only resistance to myocardial flow; the epicardial vessels are just conductance vessels that offer no resistance to myocardial flow.

In the presence of a functionally significant stenosis, classically a 70% diameter stenosis, the trans-stenotic flow drops during exertion; at a 90% diameter stenosis, the trans-stenotic flow drops at rest.

During exercise or adenosine infusion, extensive microvascular dilatation occurs, requiring an extensive increase in flow to fill the dilated circulation; since the flow cannot increase across a flow-limiting stenosis, ischemia occurs.

Supply ischemia is typically caused by $\geq 50\%$ diameter stenosis of the left main coronary artery or $\geq 70\%$ diameter stenosis of the major epicardial vessels. However, a 40-70% stenosis may be functionally significant, i.e., may impede maximal coronary flow during stress.

The functional significance of a fixed lesion depends not only on the luminal narrowing, but also on:

- **The size of the territory supplied by the vessel:** a 50% proximal LAD stenosis is often significant, whereas a 50% diagonal or distal LAD stenosis may not be.
A larger flow across a stenosis translates into a larger percentage of flow drop across the stenosis.
- **Lesion length**, as [Resistance across a stenosis = (viscosity \times length) / radius⁴] (**Poiseuille law**).
- **Amount of viable myocardium.**

Therefore, stress imaging may be useful to assess the functional significance of a borderline lesion. Also, in the cath lab, fractional flow reserve (FFR), i.e., the relative drop in flow across a lesion, may be invasively measured ⁽¹⁾.

B. Vasospastic angina (Prinzmetal angina) or dynamic coronary obstruction:

It was initially hypothesized by Prinzmetal and then demonstrated in a large series that vasospasm and vasospastic angina often occur at the site of a significant atherosclerotic obstruction in patients with significant CAD.

Vasospasm may be related to vasoconstrictors released by platelets and leukocytes at the atherosclerotic site, **or** endothelial dysfunction and abnormal vasomotor response induced by atherosclerosis.

Paradoxical vasoconstriction may occur during exercise, adrenergic stimulation (stress), or cold exposure.

Approximately 60% of patients only have symptoms at rest or mild activity without exertional limitation, sometimes in a cyclic nocturnal pattern; in those patients, angina only occurs when the dynamic component exacerbates the fixed obstruction.

On the other hand, many patients have exertional angina, whether from the CAD itself or from the exertional vasospasm, and some patients only have exertional angina.

Vasospastic angina is classically more severe than fixed- threshold angina, as the episodic obstruction is totally or subtotally occlusive, with more frequent arrhythmia, high-grade AV block, or syncope during the episodes.

While characteristically more common in women, the vasospasm occurring on top of CAD was more common in men in one series.

C. Angina secondary to severely increased demands:

This is seen with severe LVH, severe hypertension, valvular heart disease, HF, marked tachycardia, or metabolic disorders (anemia or hyperthyroidism).

Note on Coronary Flow physiology:

(1) FFR implies the assessment of pressure drop across a lesion using a coronary pressure wire; this pressure drop corresponds to a flow drop in patients with maximal microcirculatory hyperemia that exhausts autoregulation ($\text{flow} = \text{pressure} / \text{microvascular resistance}$). A flow drop $\geq 20\%$ (i.e., FFR flow ratio ≤ 0.80) implies functional significance.

Because of systolic compression of the microcirculation, the LV receives blood mainly during diastole (> 80% of the left coronary flow occurs in diastole).

Tachycardia, in addition to increasing O₂ demands, reduces myocardial O₂ supply by reducing diastolic time.

The LV coronary blood flow is directly related to the pressure gradient between DBP and LVEDP (coronary perfusion pressure) and inversely related to the microvascular resistance; the latter depends on myocardial stiffness, and, thus, on LVEDP as well (flow = delta pressure/microvascular resistance).

A reduction of DBP or an increase in LVEDP reduces coronary flow, even in the absence of a coronary stenosis.

As opposed to the LV, the RV is thin, which explains why its microcirculation is not as affected by systole as the LV's microcirculation. Approximately 50% of the right coronary-to-RV flow occurs in systole.

Since the RV receives significant flow during systole, the coronary blood flow of the RV is partly related to the gradient between SBP and RV systolic pressure, not just DBP and RVEDP.

Risk assessment and diagnosis:

The general approach for the initial diagnostic management of patients with angina and suspected obstructive CAD includes six steps as shown below. After these steps, appropriate therapies are to be initiated, which include lifestyle management, medical therapy, and revascularization when indicated.

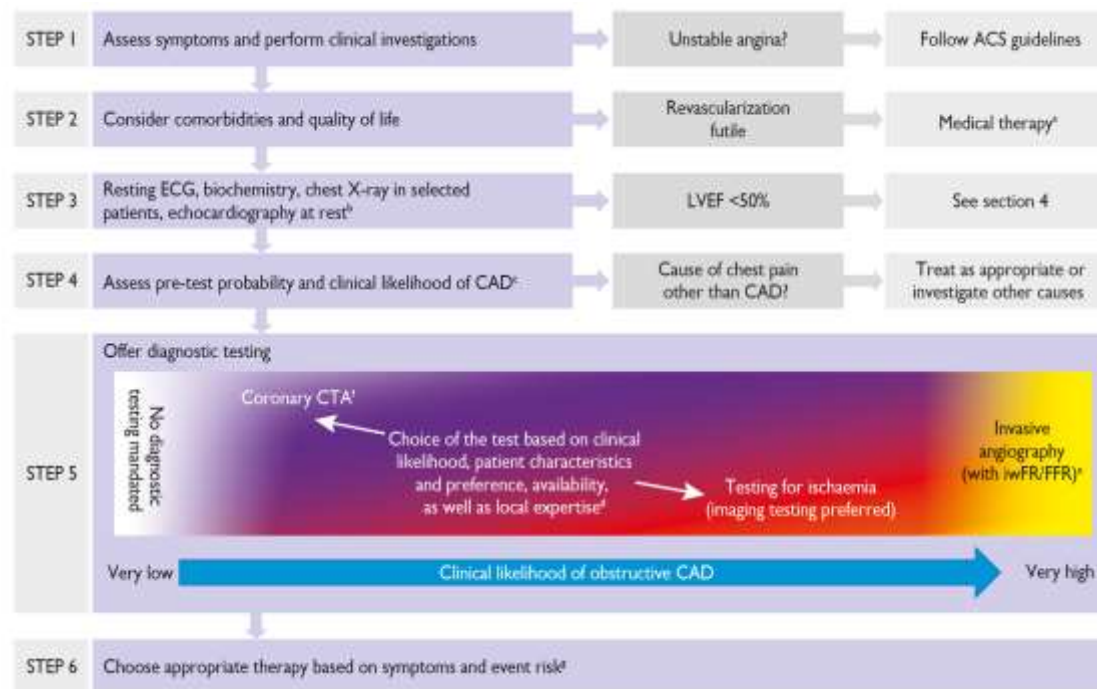


Figure 5-1: Approach for the initial diagnostic management of patients with angina and suspected coronary artery disease. **A)** If the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment may be reasonable. **B)** May be omitted in very young and healthy patients with a high suspicion of an extracardiac cause of chest pain, and in multimorbid patients in whom the echocardiography result has no consequence for further patient management. **C)** Consider exercise ECG to assess symptoms, arrhythmias, exercise tolerance, BP response, and event risk in selected patients. **D)** Ability to exercise, individual test-related risks, and likelihood of obtaining diagnostic test result. **E)** High clinical likelihood and symptoms inadequately responding to medical treatment, high event risk based on clinical evaluation (such as ST-segment depression, combined with symptoms at a low workload or systolic dysfunction indicating CAD), or uncertain diagnosis on non-invasive testing. **F)** Functional imaging for myocardial ischaemia if coronary CTA has shown CAD of uncertain grade or is non-diagnostic. **G)** Consider also angina without obstructive disease in the epicardial coronary arteries. **Source:** 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

▪ Step 1: Symptoms and signs:

- The characteristics of discomfort related to myocardial ischaemia (angina pectoris) may be divided into four categories: location, character, duration, and relationship to exertion, and other exacerbating or relieving factors.

Table 5-1: Diamond-Forrester classification of suspected anginal symptoms:

| | |
|-------------------------------|--|
| Typical angina | <i>Meets the following three characteristics:</i> <ul style="list-style-type: none"> - Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; - Precipitated by physical exertion; - Relieved by rest or nitrates within 5 min. |
| Atypical angina | <i>Meets two of these characteristics.</i> |
| Non-anginal chest pain | <i>Meets only one or none of these characteristics.</i> |

- **Unstable angina may present in one of three ways:**
 - Rest angina: pain of characteristic nature and location occurring at rest and for prolonged periods (> 20 min);
 - New-onset angina: recent (2 months) onset of moderate-to-severe angina (Canadian Cardiovascular Society grade II or III); or
 - Crescendo angina: previous angina, which progressively increases in severity and intensity, and at a lower threshold, over a short period of time.

Table 5-2: Grading of effort angina severity according to the Canadian Cardiovascular Society:

| Grade | | Description of angina severity |
|-------|--|--|
| I | Angina only with strenuous exertion | <i>Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs).</i> |
| II | Angina with moderate exertion | <i>Slight limitation of ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or</i> |

| | | |
|-----|----------------------------------|--|
| | | <i>during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions.</i> |
| III | Angina with mild exertion | <i>Having difficulties walking one or two blocks, or climbing one flight of stairs, at normal pace and conditions.</i> |
| IV | Angina at rest | <i>No exertion needed to trigger angina.</i> |

▪ **Step 2: Comorbidities and other causes of symptoms:**

Before any testing is considered, one must assess the patient's general health, comorbidities, and quality of life. If revascularization is unlikely to be an acceptable option, further testing may be reduced to a clinically indicated minimum and appropriate therapy should be instituted, which may include a trial of antianginal medication even if a diagnosis of CAD has not been fully demonstrated.

If the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment is reasonable.

▪ **Step 3: Basic testing:** Such testing can be done on an outpatient basis.

| Table 5-3: ESC Recommendation of diagnostic management of patients with suspected coronary artery disease: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Basic biochemistry testing: | | |
| <i>If evaluation suggests clinical instability or ACS, repeated measurements of troponin, preferably using high-sensitivity or ultrasensitive assays, are recommended to rule-out myocardial injury associated with ACS.</i> | I | A |
| The following blood tests are recommended in all patients: | | |
| • Full blood count (including haemoglobin); | I | B |

| | | |
|---|-----|---|
| • Creatinine measurement and estimation of renal function; | I | A |
| • A lipid profile (including LDL-C). | I | A |
| <i>It is recommended that screening for type 2 diabetes mellitus in patients with suspected and established CCS is implemented with HbA1c and fasting plasma glucose measurements, and that an oral glucose tolerance test is added if HbA1c and fasting plasma glucose results are inconclusive.</i> | I | B |
| <i>Assessment of thyroid function is recommended in case of clinical suspicion of thyroid disorders.</i> | I | C |
| Resting ECG: | | |
| <i>A resting 12 lead ECG is recommended in all patients with chest pain without an obvious non-cardiac cause.</i> | I | C |
| <i>A resting 12 lead ECG is recommended in all patients during or immediately after an episode of angina suspected to be indicative of clinical instability of CAD.</i> | I | C |
| <i>ST-segment alterations recorded during supraventricular tachyarrhythmias should not be used as evidence of CAD.</i> | III | C |
| Ambulatory electrocardiogram: | | |
| <i>Ambulatory ECG monitoring is recommended in patients with chest pain and suspected arrhythmias.</i> | I | C |
| <i>Ambulatory ECG recording, preferably monitoring with 12 lead ECG, should be considered in patients with suspected vasospastic angina.</i> | IIa | C |
| <i>Ambulatory ECG monitoring should not be used as a routine examination in patients with suspected CCS.</i> | III | C |
| Chest X-ray: | | |

| | | |
|--|------------|----------|
| <i>Chest X-ray is recommended for patients with atypical presentation, signs and symptoms of HF, or suspicion of pulmonary disease.</i> | I | C |
| Resting echocardiography and CMR: | | |
| <i>A resting transthoracic echocardiogram is recommended in all patients for:</i> <ul style="list-style-type: none"> - <i>Exclusion of alternative causes of angina;</i> - <i>Identification of regional wall motion abnormalities suggestive of CAD;</i> - <i>Measurement of LVEF for risk stratification; and</i> - <i>Evaluation of diastolic function.</i> | I | B |
| <i>Ultrasound of the carotid arteries should be considered, and be performed by adequately trained clinicians, to detect plaque in patients with suspected CCS without known atherosclerotic disease.</i> | IIa | C |
| <i>CMR may be considered in patients with an inconclusive echocardiographic test.</i> | IIb | C |

▪ **Step 4: Assessment of pre-test probability and clinical likelihood of CAD:**

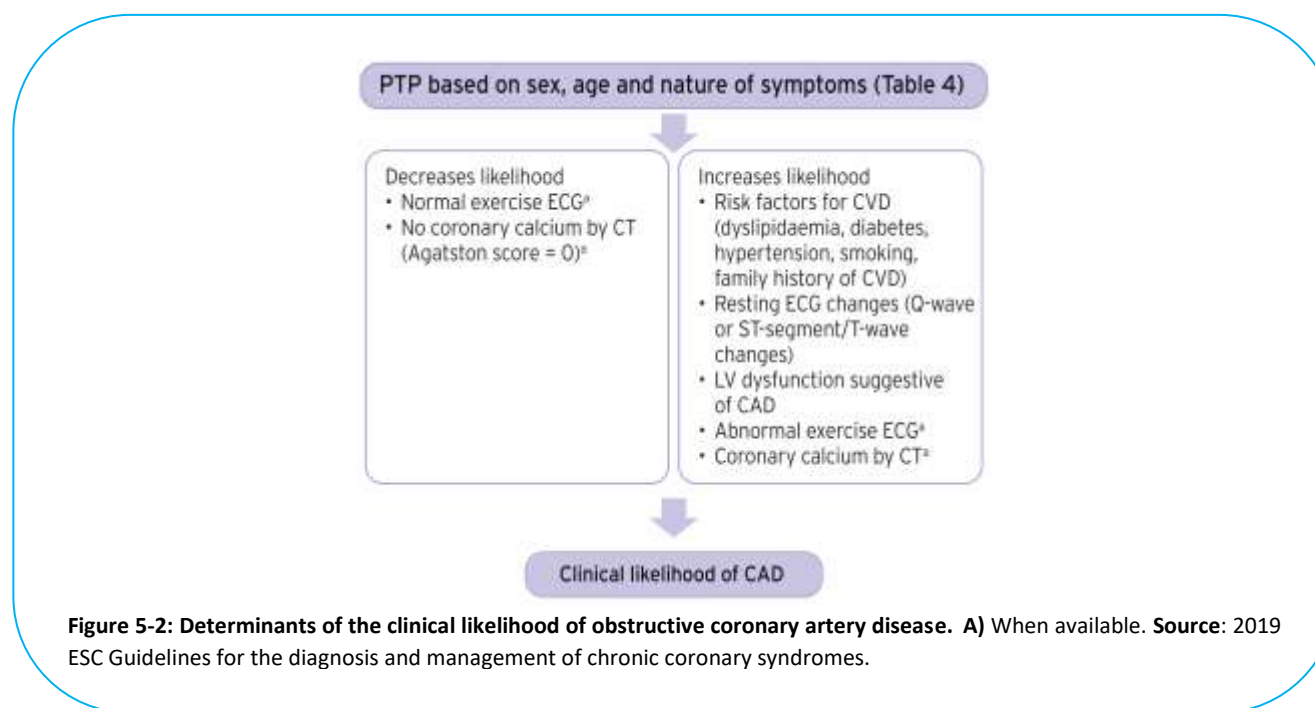
The likelihood of obstructive CAD is influenced by the prevalence of the disease in the population studied, as well as by clinical features of an individual patient. A simple predictive model can be used to estimate the pre-test probability (PTP) of obstructive CAD (based on age, sex, and the nature of symptoms) substantially reduce the need for non-invasive and invasive tests in patients with suspected stable CAD.

| Table 5-4: Pre-test probabilities of obstructive coronary artery disease: | | | | | | | | |
|--|----------------|--------------|-----------------|--------------|--------------------|--------------|-------------------------------|--------------|
| Age | Typical | | Atypical | | Non-anginal | | Dyspnea ⁽¹⁾ | |
| | Men | Women | Men | Women | Men | Women | Men | Women |
| 30-39 | 3% | 5% | 4% | 3% | 1% | 1% | 0% | 3% |
| 40-49 | 22% | 10% | 10% | 6% | 3% | 2%% | 12% | 3% |

(1) In addition to the classic Diamond and Forrester classes, patients with dyspnea only are included.

| | | | | | | | | |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|
| 50-59 | 32% | 13% | 17% | 6% | 11% | 3% | 20% | 9% |
| 60-69 | 44% | 16% | 26% | 11% | 22% | 6% | 27% | 14% |
| 70+ | 52% | 27% | 34% | 19% | 24% | 10% | 32% | 12% |

The region shaded dark denote the groups in which non-invasive testing is most beneficial (PTP > 15%). The regions shaded lighter denote the groups with PTPs of CAD between 5-15%, in which testing for diagnosis may be considered after assessing the overall clinical likelihood based on the modifiers of PTPs presented in the following figure.



▪ **Step 5: Selecting appropriate testing:**

Either a functional or anatomical test can be used to establish a diagnosis of obstructive CAD.

- Coronary CTA is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality.
- Functional non-invasive testing may be preferred in patients at the higher end of the range of clinical likelihood if revascularization is likely or the patient has previously diagnosed CAD. In addition to diagnostic accuracy and clinical likelihood, the selection of a non-invasive test depends on other patient characteristics, local expertise, and the availability of tests.
- For diagnostic purposes, ICA is only necessary in patients with suspected CAD in cases of inconclusive non-invasive testing or, exceptionally, in patients from particular professions, due to regulatory issues. However, ICA may be indicated if non-invasive assessment suggests high event risk for determination of options for revascularization.

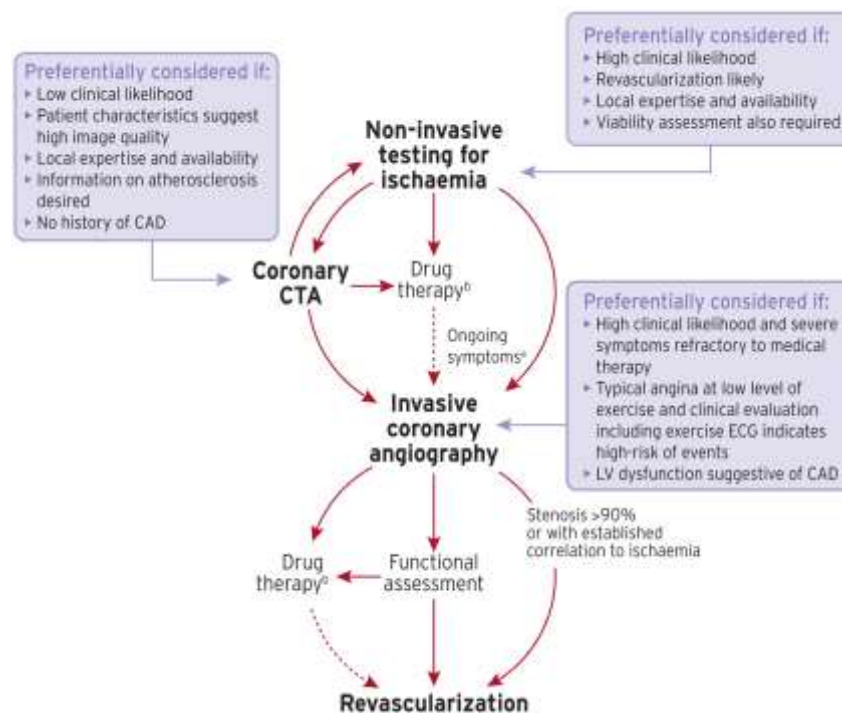


Figure 5-3: Main diagnostic pathways in symptomatic patients with suspected obstructive coronary artery disease. Depending on clinical conditions and the healthcare environment, patient workup can start with either of three options: non-invasive testing, coronary CT angiography, or invasive coronary angiography. Through each pathway, both functional and anatomical information is gathered to inform an appropriate diagnostic and therapeutic strategy. Risk-factor modification should be considered in all patients. **A)** Consider microvascular angina. **B)** Antianginal medications and/or risk-factor modification. **Source:** 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

Table 5-5: ESC recommendations for Initial diagnostic management of symptomatic patients with suspected CAD:

Recommendations

Class Level

| Exercise ECG: | | |
|---|------------|----------|
| <i>Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients. ⁽¹⁾</i> | I | C |
| <i>Exercise ECG may be considered</i> | | |
| <i>- as an alternative test to rule-in and rule-out CAD when non-invasive imaging is not available.</i> | IIb | B |
| <i>- in patients on treatment to evaluate control of symptoms and ischaemia.</i> | IIb | C |
| <i>Exercise ECG is not recommended for diagnostic purposes in patients with ≥ 0.1 mV ST segment depression on resting ECG <u>or</u> who are being treated with digitalis.</i> | III | C |
| Diagnostic imaging: | | |
| <i>Non-invasive functional imaging for myocardial ischaemia ⁽²⁾ or coronary CTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.</i> | I | B |
| <i>It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance ⁽³⁾, local expertise, and the availability of tests.</i> | I | C |
| <i>Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance <u>or</u> is not diagnostic.</i> | I | B |
| <i>Invasive coronary angiography is recommended as an alternative test to diagnose CAD in patients with: (i) a high clinical likelihood, (ii) severe symptoms refractory to medical</i> | I | B |

(1) When this information will have an impact on diagnostic strategy or management.

(2) Stress echocardiography, stress CMR, single-photon emission CT, or positron emission tomography.

(3) Characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.

| | | |
|--|------------|----------|
| <i>therapy or typical angina at a low level of exercise, and (iii) clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenosis before revascularization, unless very high grade (> 90% diameter stenosis).</i> | | |
| <i>Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.</i> | IIa | B |
| <i>Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.</i> | IIa | C |
| <i>Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely.</i> | III | C |
| <i>Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD.</i> | III | C |

▪ **Step 6: Assessment of event risk:**

Assessment of event risk is recommended in every patient being evaluated for suspected CAD or with a newly diagnosed CAD, as it has major impacts on therapy decisions. The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms.

| Table 5-6: Definitions of high event risk for different test modalities in patients with established CCS: | |
|--|--|
| Exercise ECG | <i>CV mortality > 3% per year according to Duke Treadmill Score</i> |
| SPECT or PET perfusion imaging | <i>Area of ischaemia ≥ 10% of the LV myocardium</i> |

| | |
|------------------------------------|---|
| Stress echocardiography | ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia |
| Cardiac MRI | ≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments |
| Coronary CTA or ICA | Three-vessel disease with proximal stenoses, LM disease, or proximal LAD disease |
| Invasive functional testing | $FFR \leq 0.8$, $iwFR \leq 0.89$ |

Table 5-7: ESC Recommendations on risk assessment

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Risk stratification is recommended based on clinical assessment and the result of the diagnostic test initially employed to diagnose CAD.</i> | I | B |
| <i>Resting echocardiography is recommended to quantify LV function in all patients with suspected CAD.</i> | I | C |
| <i>Risk stratification, preferably using stress imaging or coronary CTA (if permitted by local expertise and availability), or alternatively exercise stress ECG (if significant exercise can be performed and the ECG is amenable to the identification of ischaemic changes), is recommended in patients with suspected or newly diagnosed CAD.</i> | I | B |
| <i>In symptomatic patients with a high-risk clinical profile, ICA complemented by invasive physiological guidance (FFR) is recommended for CV risk stratification, particularly if the symptoms are responding inadequately to medical treatment and revascularization is considered for improvement of prognosis.</i> | I | A |
| <i>In patients with mild or no symptoms, ICA complemented by invasive physiological guidance (FFR/iwFR) is recommended for patients on medical treatment, in whom non</i> | I | A |

| | | |
|--|------------|----------|
| <i>invasive risk stratification indicates a high event risk and revascularization is considered for improvement of prognosis.</i> | | |
| <i>ICA complemented by invasive physiological guidance (FFR) should be considered for risk-stratification purposes in patients with inconclusive or conflicting results from non-invasive testing.</i> | IIa | B |
| <i>If coronary CTA is available for event risk stratification, additional stress imaging should be performed before the referral of a patient with few/no symptoms for ICA.</i> | IIa | B |
| <i>Echocardiographic assessment of global longitudinal strain provides incremental information to LVEF and may be considered when LVEF is > 35%.</i> | IIb | B |
| <i>Intravascular ultrasound (IVUS) may be considered for the risk stratification of patients with intermediate LM stenosis.</i> | IIb | B |
| <i>ICA is not recommended solely for risk stratification.</i> | III | C |

N.B: Warranty periods:

When should stress testing be repeated in patients with prior negative studies who present with chest pain?

Stress tests have “warranty periods” during which the risk of CV events is low (< 1% per year) and during which there is no need to perform a coronary angiogram unless the patient has objective evidence of new CAD, such as ACS with positive cardiac markers or new, severe ischemia on the ECG.

- Normal stress test (given adequate stress): 1 year
- Normal coronary angiogram: 2 years
- CCTA with no stenosis or plaque: 2 years

Treatment:

A. Lifestyle management

B. Pharmacological treatment:

- **Anti-ischemic drugs:** B-blockers - CCBs - Nitrates - Ivabradine - Nicorandil - Ranolazine - Trimetazidine
- **Event prevention:** Antiplatelet drugs - Lipid lowering agents - RAAS blockers.

C. Revascularization.

A. Lifestyle Management: Implementing healthy lifestyle behaviours decreases the risk of subsequent CV events and mortality. Benefits are evident as early as 6 months after an index event.

- **Smoking:**

- Smoking cessation leads to a 50% reduction of the excessive risk of MI and stroke within 1 year (mostly within 2 months). At 3-5 years, the risk approaches that of never-smokers.
- Quitting smoking is complex because smoking is both pharmacologically and psychologically highly addictive. Nicotine replacement therapy is safe in patients with CAD and should routinely be offered.
Bupropion and varenicline have been found safe to use in patients with stable CAD in some studies, although the safety of varenicline has recently been questioned in a meta-analysis, being associated with statistically significant increase in CVD.

- **Diet:**

- Increase consumption of fruits and vegetables (≥ 200 g each per day).
- 35-45 g of fibre per day, preferably from wholegrains.
- Moderate consumption of nuts (30 g per day, unsalted).
- 12 servings of fish per week (one to be oily fish).
- Limited lean meat, low-fat dairy products, and liquid vegetable oils.
- Saturated fats to account for $< 10\%$ of total energy intake; replace with polyunsaturated fats.

- As little intake of trans unsaturated fats as possible, preferably no intake from processed food, and < 1% of total energy intake.
- ≤ 5 -6 g of salt per day.
- If alcohol is consumed, limiting intake to ≤ 100 g/week or < 15 g/day is recommended.
- Avoid energy-dense foods such as sugar-sweetened soft drinks.
- **Physical activity:**
 - Patients with previous acute MI, CABG, PCI, stable angina or stable chronic heart failure should undergo moderate-to-vigorous intensity aerobic exercise training ≥ 3 times a week and for 30 min per session.
 - In patients with significant CAD who are not candidates for revascularization, exercise training may offer an alternative means of symptom alleviation and improved prognosis.
- **Sexual activity:**
 - Sexual activity is associated with an exercise workload of up to 6 METS (1 MET= 3.5 mL oxygen consumption/kg/min) depending on the type of activity. Sexual activity may thus trigger ischaemia, and nitroglycerin prior to sexual intercourse may be helpful as in other physical activity.
 - Patients with mild angina, successful coronary revascularization and NYHA Class I heart failure generally do not need specific evaluation before resuming sexual activity.
 - Patients with more symptomatic heart disease, including moderate angina, may be guided by an exercise stress test as a means of assessing risk and reassuring the patient.
 - Exercise training should be advocated to improve exercise capacity and reduce myocardial oxygen consumption during sexual activity.
 - The common denominator between erectile dysfunction and CAD is endothelial dysfunction and antihypertensive drugs -in particular b-blockers and thiazides- increases the risk of erectile dysfunction.
 - Lifestyle and pharmacological intervention -including weight loss, exercise training, smoking cessation and statin treatment- ameliorate ED.

Pharmacological therapy with phosphodiesterase type 5 (PDE5) inhibitors are effective, safe and well tolerated in men with stable CAD. However, use of nitric oxide donors, i.e. all of the preparations of nitroglycerin are absolute contra-indications to the use of PDE5 inhibitors because of the risk of synergistic effects on vasodilation, causing hypotension and haemodynamic collapse.

PDE5 inhibitors are not recommended in patients with low blood pressure, with severe heart failure (NYHA III-IV), refractory angina or recent CV events.

Patients must be informed about the potentially harmful interactions between PDE5 inhibitors and nitrates.

If a patient on a PDE5 inhibitor develops chest pain, nitrates should not be administered in the first 24 hours (sildenafil, vardenafil) to 48 hours (tadalafil).

- **Weight management:**

- Both overweight and obesity are associated with an increased risk of death in CAD. Weight reduction in overweight and obese people is recommended in order to achieve favourable effects on BP, dyslipidaemia and glucose metabolism.
- The presence of sleep apnoea symptoms should be carefully assessed, especially in obese patients. Sleep apnoea has been associated with an increase in CV mortality and morbidity.

- **Lipid management:**

- Patients with established CAD are regarded as being at very high risk for CV events and statin treatment should be considered, irrespective of low density lipoprotein cholesterol (LDL-C) levels.
- The goals of treatment are LDL-C < 55 mg/dL and > 50% LDL-C reduction.
- For patients undergoing PCI for CCS, high dose atorvastatin has been shown to reduce the frequency of peri-procedural MI in both statin-naïve patients and patients receiving chronic statin therapy. Thus, reloading with high intensity statin before PCI may be considered.

- **Arterial Hypertension Management.**

- **Diabetes and other disorders:**

- DM is a strong risk factor for CV complications, increases the risk of progression of coronary disease and should be managed carefully, with good control of HbA1c to < 7.0% generally, and < 6.5-6.9% on an individual basis.
- ACE-inhibitor or ARBs should always be included because of the renal protective effects.
- Patients with chronic kidney disease (CKD) are at high risk and particular care should be taken to address risk factors and achieve BP and lipid targets.
- The BP target in patients with CAD and diabetes is to be < 140/85 mmHg.
- Statins are generally well tolerated in CKD stages 1-2 (GFR < 60-89 mL/min/1.73 m²) whereas, in CKD stages 3–5, statins with minimal renal excretion should be chosen (atorvastatin, fluvastatin, pitavastatin, rosuvastatin).

| Table 5-8: ESC Recommendations on lifestyle management | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.</i> | I | A |
| <i>Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.</i> | I | A |
| <i>Exercise-based cardiac rehabilitation is recommended as an effective means for patients with CCS to achieve a healthy lifestyle and manage risk factors.</i> | I | A |
| <i>Involvement of multidisciplinary healthcare professionals (e.g. cardiologists, GPs, nurses, dieticians, physiotherapists, psychologists, and pharmacists) is recommended.</i> | I | A |
| <i>Psychological interventions are recommended to improve symptoms of depression in patients with CCS.</i> | I | B |
| <i>Annual influenza vaccination is recommended for patients with CCS, especially in the elderly.</i> | I | B |

B. Pharmacological management:

The aims of pharmacological management of CCS patients are to reduce angina symptoms and exercise-induced ischaemia, and to prevent CV events. There is no universal definition of an optimal treatment in patients with CCS, and drug therapies

must be adapted to each patient's characteristics and preferences. Initial drug therapy usually consists of one or two antianginal drugs, as necessary, plus drugs for secondary prevention of CVD.

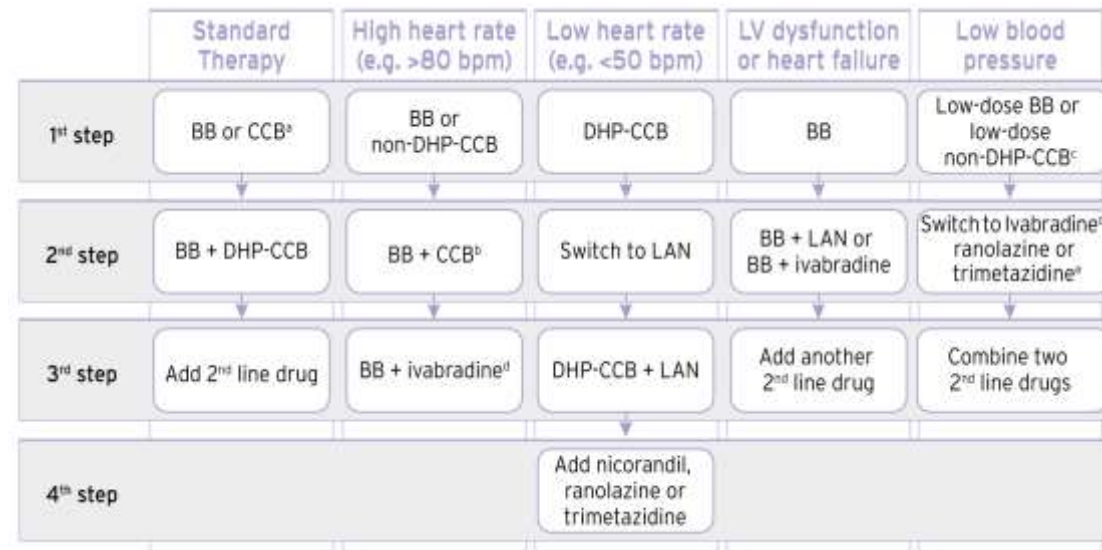


Figure 5-4: Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. **A)** Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step; **B)** The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure; **C)** Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure; **D)** *Ivabradine should not be combined with non-DHP-CCB*; **E)** Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged. **Source:** 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

1. Anti-ischaemic drugs:

- **B-blockers:**

- B-blockers act directly on the heart to reduce heart rate, contractility, and ectopic activity. Additionally, they may increase perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas.
- In patients with established CAD and angina, β -blockers are titrated to achieve a resting heart rate of 55-60 bpm. This tight rate control has not been associated with improved outcomes in hypertension and is not pursued when β -blockers are used solely for hypertension control.

Because they have been shown to reduce mortality after MI, β -blockers are the first line therapy for angina. However, in stable CAD without prior MI or HF, there is no evidence of mortality reduction and the main benefit is angina relief.

- Myocardial β_1 -receptors have a positive inotropic and chronotropic effect, thus increasing myocardial O_2 demands. β_2 -Receptors mainly have a vasodilatory and bronchodilatory effect, with a limited inotropic and chronotropic effect at baseline. However, the latter effect is exaggerated when β_1 -receptors are blocked. Thus, β_2 -blockade may be useful in patients requiring a comprehensive blockade of all myocardial adrenergic receptors, such as HF (carvedilol), but may induce a harmful vasoconstrictive and bronchospastic effect.
- Nebivolol and bisoprolol are partly secreted by the kidney, whereas carvedilol and metoprolol are metabolized by the liver, hence being safer in patients with renal compromise.

- **Doses:**

Metoprolol tartrate 25 mg BID, titrated every 3-7 days to 50-100 mg BID (max 200 mg BID).

Metoprolol succinate: the once-daily dose is equivalent to the total daily dose of metoprolol tartrate.

Atenolol 12.5-25 mg BID (or Qday in advanced renal failure), titrated up to 50 mg BID.

Carvedilol: 3.125-25 mg BID; labetalol 100-400 mg BID.

N.B:

Severe PAD was considered a relative contraindication to non-selective β -blockers, because of an initial β_2 -blocker

vasoconstrictive effect. However, this is no longer a contraindication to β -blockers, as they proved safe in patients with PAD. Also, PAD patients often die of CAD, and thus, β -blockers are valuable in the PAD setting.

In diabetic patients, metoprolol appears to slightly worsen diabetes control (HbA1c). This is not the case with carvedilol and nebivolol, which should be the preferred β -blockers in those patients (GEMINI trial).

- **Calcium channel blockers:**

Non-dihydropyridines (non-DHPs): decrease cardiac inotropism and chronotropism and have a vasodilatory effect (afterload reduction). Also, they dilate the coronary arteries.

- Examples: diltiazem and verapamil. Verapamil has more negative inotropic effect, slightly more AV and SA nodal depressant effect, and stronger vasodilatory effect than diltiazem.
- Doses: diltiazem 30-90 mg TID-QID, diltiazem CD 120-480 mg Qday; verapamil 80-120 mg TID-QID, verapamil SR 180-480 mg/d.

Dihydropyridines (DHPs): are vasodilators that reduce afterload and vasodilate the coronary arteries.

- Only the long-acting formulations are used. Short-acting DHPs may cause reflex tachycardia, which leads to ischemia.
- Except for nifedipine, DHPs are not contraindicated in bradycardia or HF ⁽¹⁾.
- DHPs are the first-choice antianginal therapy in patients with bradycardia or AV block, and are the second choice in patients already on β -blockers.
- Examples: amlodipine, felodipine, and nifedipine XL.
- Doses: amlodipine 2.5-10 mg Qday (same for felodipine); nifedipine XL 30-90 mg Qday.

- **Nitrates:**

- Nitrates are venodilators and thus reduce ischemia primarily by reducing preload. They also improve coronary flow by reducing intramyocardial diastolic tension, i.e., LVEDP. They are also, to a lesser extent, arterial vasodilators and thus reduce afterload. The dilatation of epicardial coronary arteries is a less important anti-ischemic mechanism than preload reduction, but dilatation of collaterals may be particularly useful.

(1) *Nifedipine has some negative inotropic effects and should not be used in HF; other DHPs have minimal to no negative inotropic effects.*

Vasodilators, in general, may worsen myocardial ischemia in critical CAD as they increase flow through the normal coronary arteries at the expense of the abnormal artery that cannot dilate, creating a coronary steal phenomenon through collaterals (e.g., adenosine). This, however, does not usually happen with nitrates as they do not drastically affect the microvascular tone, and thus do not drastically increase coronary flow to the normal myocardium.

- While sublingual nitroglycerin is used as needed (during angina or before exertion) and has a short effect < 5 min, long-acting formulations are used as adjunct to background β -blocker or CCBs therapy:
Isosorbide dinitrate 10-40 mg TID, isosorbide mononitrate 30-240 mg Qday, NTG paste 0.5-2 inches TID, NTG patch 0.2–0.6 mg/h Q24h.
- Worsening of endothelial dysfunction is a potential complication of long-acting nitrates, hence the common practice of the routine use of long-acting nitrates as first line therapy for patients with effort angina needs re-evaluation.
- **Side-effects:** Hypotension is the most serious, and headache the most common side-effect of nitrates (aspirin may relieve these). Failure of therapy: includes nitric oxide resistance and nitrate tolerance.
- **Ivabradine:**
 - Ivabradine is a heart rate-lowering agent selectively inhibiting the sinus node I(f) pacemaking current, thereby decreasing the myocardial oxygen demand without effect on inotropism or BP.
 - It was approved by the European Medicines Agency (EMA) for chronic stable angina in patients intolerant to or inadequately controlled by β -blockers and whose heart rate > 60 b.p.m. (in sinus rhythm). Ivabradine is thus an effective anti-anginal agent, alone or in combination with β -blockers.
- **Nicorandil:**
 - Nicorandil is a nitrate derivative of nicotinamide that can be used for the prevention and long-term treatment of angina, and may be added after β -blockers and CCBs. It is EMA but not FDA approved.
 - Nicorandil dilates epicardial coronary arteries and stimulates ATP-sensitive potassium channels (K_{ATP}) in vascular smooth muscles.
 - Long-term use of oral nicorandil may stabilize coronary plaque in patients with stable angina.

- Occasional side-effects include: oral, intestinal and perianal ulceration.
- **Ranolazine:**
 - Ranolazine is a selective inhibitor of late sodium current with anti-ischaemic and metabolic properties.
 - Doses of 500-2000 mg daily reduced angina and increased exercise capacity without changes in heart rate or BP.
 - The EMA approved ranolazine in 2009 for add-on treatment in stable angina in patients inadequately controlled by or intolerant to first-line agents (beta-blockers and/ or calcium antagonists).
 - These results suggest that this drug can be added to other well-established anti-anginal drugs, in particular in patients with higher HbA1c levels, who may also more often rely on medical management.
 - Ranolazine plasma levels increase with CYP3A inhibitors (Non DHB-CCBs, macrolides, grapefruit juice).
 - Ranolazine clearance is reduced by renal and hepatic impairment.
 - Ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT-prolonging drugs.
- **Trimetazidine:**
 - Trimetazidine is an anti-ischaemic metabolic modulator, works by inhibiting a specific enzyme called long-chain 3-ketoacyl-CoA thiolase, which is involved in the beta-oxidation process of fatty acids. By blocking this enzyme, trimetazidine reduces the fatty acids oxidation and promotes the oxidation of glucose instead.
 - It has similar anti-anginal efficacy to propranolol in doses of 20 mg twice daily.
 - Trimetazidine (35 mg twice daily) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia.
 - It is contraindicated in Parkinson's disease and motion disorders [such as tremor (shaking), muscle rigidity and walking disorders and restless leg syndrome].
 - In diabetic persons, trimetazidine improved HbA1c and glycaemia.

Table 5-9: ESC Recommendations on anti-ischaemic drugs in patients with chronic coronary syndromes:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--------------------------------|--------------|--------------|
| General considerations: | | |

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|---|------------|----------|
| <i>Medical treatment of symptomatic patients requires one or more drug(s) for angina/ischaemia relief in association with drug(s) for event prevention.</i> | I | C |
| <i>It is recommended that patients are educated about the disease, risk factors, and treatment strategy.</i> | I | C |
| <i>Timely review of the patient's response to medical therapies (e.g. 2-4 weeks after drug initiation) is recommended.</i> | I | C |
| Angina/ischaemic relief: | | |
| <i>Short-acting nitrates are recommended for immediate relief of effort angina.</i> | I | B |
| <i>First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms.</i> | I | A |
| <i>If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered.</i> | IIa | C |
| <i>Initial first-line treatment with the combination of a beta-blocker and a DHP-CCB should be considered.</i> | IIa | B |
| <i>Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms.</i> | IIa | B |
| <i>When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.</i> | IIa | B |
| <i>Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.</i> | IIa | B |

| | | |
|---|------------|----------|
| <i>In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance.</i> | IIb | C |
| <i>In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance.</i> | IIb | B |
| <i>Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy or co-administration of phosphodiesterase inhibitors.</i> | III | B |

2. Event prevention:

- **Antiplatelet agents:**

- **Low-dose aspirin:**

- Aspirin remains the cornerstone of pharmacological prevention of arterial thrombosis. It acts via irreversible inhibition of platelet cyclooxygenase-1 (COX-1) and thus thromboxane production, which is normally complete with chronic dosing ≥ 75 mg/day.
- Contrary to the antiplatelet effects, the GI side-effects of aspirin increase at higher doses. The optimal risk-benefit ratio appears to be achieved with an aspirin dosage of 75-150 mg/day.

- **P2Y₁₂ inhibitors:**

- P2Y₁₂ inhibitors act as antagonists of the platelet adenosine diphosphate (ADP) receptor P2Y₁₂, thereby inhibiting platelet aggregation.
- The major study supporting the use of P2Y₁₂ inhibitors in stable coronary patients is the (CAPRIE) trial, which showed an overall benefit of clopidogrel as compared with aspirin in preventing CV events in three categories of patients with previous MI, previous stroke or peripheral vascular disease.
- Clopidogrel should thus be proposed as a second-line treatment, esp. for aspirin-intolerant CVD patients.

- Prasugrel and ticagrelor are new P2Y₁₂ antagonists that achieve greater platelet inhibition, compared with clopidogrel. Prasugrel and ticagrelor are both associated with a significant reduction of CV outcomes as compared with clopidogrel in ACS patients, but no clinical studies have evaluated the benefit of these drugs in CCS patients.
- **Combination of antiplatelet agents:** Dual antiplatelet therapy (DAPT) is the standard of care for patients with ACS, including after the acute phase, when the patients are stabilized, or in CCS patients who have undergone elective PCI. However, in (CHARISMA) study, DAPT did not confer benefit in patients with stable vascular disease or at risk of atherothrombotic events.
- **Poor response to antiplatelet agents:** The influence of genetic variants on the response to antiplatelet agents, especially clopidogrel, has been well established in patients with ACS and planned PCI, but not in patients with stable CAD. However, there is currently no recommendation to perform genetic testing in patients with stable CAD. Platelet function testing in CCS patients undergoing PCI is not recommended as a routine.
- **Lipid-lowering agents:** Patients with documented CAD are regarded as being at very high risk and should be treated with statins. The treatment target is LDL-C < 55 mmol/L and > 50% reduction.
- **ACEIs:** it is appropriate to consider ACE inhibitors for the treatment of patients with CCS, especially with co-existing hypertension, LVEF ≤ 40%, diabetes or CKD, unless contraindicated. However, not all clinical trials have demonstrated that the ACE inhibitors reduce all-cause mortality, CV mortality, non-fatal MI, stroke and heart failure in patients with atherosclerosis and preserved LV function.
- **Aldosterone antagonists (spironolactone or eplerenone)** are recommended for use in post-MI patients without significant renal dysfunction or hyperkalaemia, who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have an LVEF ≤ 40% and have either diabetes or heart failure.

N.B: Use of Analgesics in CCS:

The use of selective cyclooxygenase-2 (COX-2) inhibitors and traditional NSAIDs has been associated with an increased risk for CV events in clinical trials in arthritis and cancer prevention and are not recommended.

In patients at increased CV risk in need of pain relief, it is therefore recommended to commence with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs.

If adequate pain relief requires the use of NSAIDs, these agents should be used in the lowest effective doses and for the shortest possible duration. Naproxen has been reported to be the NSAID with the lowest CV risk, but is associated with a higher risk of GI bleeding than the COX2 inhibitors and the other non-selective NSAIDs.

In patients with atherosclerotic vascular disease -and in CCS in particular- NSAID treatment should, when this is indicated for other reasons, be combined with low-dose aspirin to ensure effective platelet inhibition.

| Table 5-10: ESC Recommendations for event prevention: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Antithrombotic therapy in patients with CCS and in sinus rhythm: | | |
| <i>Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization.</i> | I | A |
| <i>Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.</i> | I | B |
| <i>Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic <u>or</u> asymptomatic patients, with either PAD or a history of ischaemic stroke or TIA.</i> | IIb | B |
| <i>Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.</i> | IIb | C |
| <i>Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events ⁽¹⁾ and without high bleeding risk ⁽²⁾.</i> | IIa | A |
| <i>Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischaemic events and without high bleeding risk.</i> | IIb | A |

(1) Diffuse multivessel CAD with at least one of the following: DM requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m².

(2) Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent GI bleeding or anaemia due to possible GI blood loss, other GI pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR < 15 mL/min/1.73 m²

| | | |
|--|-----|---|
| Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm: | | |
| Aspirin 75-100 mg daily is recommended following stenting. | I | A |
| <p>Clopidogrel 75 mg daily following appropriate loading (e.g., 600 mg or > 5 days of maintenance therapy)</p> <ul style="list-style-type: none"> - is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type. - should be considered for 3 months only in patients with a higher risk of life-threatening bleeding. - may be considered for 1 month only in patients with very high risk of life-threatening bleeding. | I | A |
| | IIa | A |
| | IIb | C |
| Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance. | IIb | C |
| Antithrombotic therapy in patients with CCS and AF: | | |
| When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a VKA. | I | A |
| <p>Long-term OAC therapy (NOAC or VKA with time in therapeutic range > 70%)</p> <ul style="list-style-type: none"> - is recommended in patients with AF and a CHA₂DS₂-VASc score ≥ 2 in males and ≥ 3 in females. - should be considered in patients with AF and a CHA₂DS₂-VASc score of 1 in males and 2 in females. | I | A |
| | IIa | B |
| Aspirin 75-100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events who do not have a high bleeding risk. | IIb | B |
| Antithrombotic therapy in post-PCI patients with indication for OAC: | | |

| | | |
|---|------------|----------|
| <i>It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.</i> | I | C |
| <i>In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) is used in preference to a VKA in combination with antiplatelet therapy.</i> | I | A |
| <i>When there is concerns about high bleeding risk prevail over concerns about stent thrombosis ⁽¹⁾ or ischaemic stroke ⁽²⁾,</i> <i>- Rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d.</i> <i>- Dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy.</i> | IIa | B |
| <i>After uncomplicated PCI, early cessation (≤ 1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, irrespective of the type of stent used.</i> | IIa | B |
| <i>Triple therapy with aspirin, clopidogrel, and an OAC for ≥ 1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤ 6 months) decided according to assessment of these risks and clearly specified at hospital discharge.</i> | IIa | C |

(1) Risk of stent thrombosis encompasses (i) the risk of thrombosis occurring and (ii) the risk of death if stent thrombosis occurs, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length > 60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

(2) Congestive HF, hypertension, age ≥ 75 years (2 points), diabetes, prior stroke/transient ischaemic attack/embolus (2 points), vascular disease (CAD on imaging or angiography, prior MI, PAD, or aortic plaque), age 65-74 years, and female sex.

| | | |
|--|------------|----------|
| <i>In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target INR in the range of 2.0-2.5 and with time in therapeutic range > 70%.</i> | IIa | B |
| <i>Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.</i> | IIb | C |
| <i>The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.</i> | III | C |
| Use of proton pump inhibitors: | | |
| <i>Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of GI bleeding.</i> | I | A |
| Lipid-lowering drugs: | | |
| <i>Statins are recommended in all patients with CCS.</i> | I | A |
| <i>If a patient's goal ⁽¹⁾ is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.</i> | I | B |
| <i>For patients at very high risk who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.</i> | I | A |
| ACE inhibitors: | | |
| <i>ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).</i> | I | A |
| <i>ACE inhibitors should be considered in CCS patients at very high risk of CV events.</i> | IIa | A |
| Other drugs: | | |

(1) The treatment goals are shown in the ESC/EAS Guidelines for the management of dyslipidaemias.

| | | |
|--|------------|----------|
| <i>Beta-blockers are recommended in patients with LV dysfunction or systolic HF.</i> | I | A |
| <i>In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.</i> | IIa | B |

C.Revascularization:

- **Objective and Indications:**

- In patients with CCS, optimal medical therapy is key for reducing symptoms, halting the progression of atherosclerosis, and preventing atherothrombotic events.
- The indications for revascularization in patients with CCS who receive optimal medical treatment are:
 - Persistence of symptoms despite medical treatment (COURAGE and FAME 2 trials) and/or
 - Improvement of prognosis: In CCS, the prognostic benefit is dependant on the extent of myocardium subject to ischemia. With the exception of subtotal stenosis in a major coronary vessel, angiography alone does not suffice to establish the indication for PCI, but documentation of ischemia or hemodynamic relevance is required. Based on 2019 ESC guidelines: Whether patients are symptomatic or not, revascularization should be considered in the following scenarios: LVEF \leq 35% due to CAD, in case of multivessel disease, severe stenosis (> 90% diameter), persistent angina, or large ischemia (ischemia > 10% in asymptomatic patients).

To date, no clinical trial has shown a benefit of PCI over OMT alone on survival. In case of left main disease, data have shown a survival benefit of revascularization with CABG compared to medical treatment.

- **Revascularization strategies:**

- **CABG vs. PCI in left main disease:**

- Guidelines used to advocate CABG surgery as Class I indication for myocardial revascularization in patients with left main disease. However, more recent RCTs and registry studies support PCI as a reasonable alternative in selective patients with less complex LMCA disease.

- ESC guidelines recommend PCI in LM disease with SYNTAX score ≤ 22 (class I) and SYNTAX score 23-32 (class IIa). PCI is not recommended in LM disease SYNTAX score ≥ 33 .
- ACC guidelines recommend PCI in selected patients with CCS and significant LMCA disease for whom PCI can provide equivalent revascularization to that possible with CABG, PCI is reasonable to improve survival (Class IIa).
- **CABG vs. PCI in multivessel disease:** Patients with complex three-vessel coronary artery disease have been found to have better outcomes with CABG than with PCI, especially in the case of DM. When coronary lesions are less extensive (defined by a SYNTAX score ≤ 22), PCI is recommended equally to CABG in non-diabetic patients. CABG is beneficial in these patients irrespective of LV function, but more so in the case of mild LV dysfunction with EF 35-50% **or** evidence of moderate/severe ischemia on stress testing (i.e., make sure CAD is functionally significant).
Note that the survival benefit in stable CAD does not emerge until 2 years after CABG, partly because of the early surgical hazard; thus, CABG is an appropriate therapy in patients who are otherwise likely to have a good longevity.
- **Reasons for superiority of CABG vs. PCI:**
 - CABG success is much less affected by the anatomical complexity (e.g., CTO) and the diffuseness of CAD.
 - While PCI treats focal disease, a graft improves flow to the whole coronary territory, including segments with moderate diffuse disease, and protects from MI resulting from occlusion of the proximal coronary segment. Hence, CABG is consistently associated with a lower risk of MI and angina recurrence than PCI. Even when MI occurs after CABG, it is less likely to be fatal and more likely a small MI, as compared with patients receiving medical therapy or PCI.
 - Very long longevity of LIMA graft.
 - More complete revascularization ⁽¹⁾ with CABG (vessels with CTO are sometimes left untreated in a multivessel PCI strategy).
- **Hybrid CABG-PCI:**
 - The superiority of CABG mainly results from the longevity of the LIMA-to-LAD graft.
 - DES stenting of non-LAD vessels, when feasible, is likely equal or superior results to placement of venous grafts, ~25% of which occlude by the first year.

(1) Complete revascularization is defined as revascularization of all functionally significant stenoses in vessels ≥ 1.5 mm supplying viable territories.

- The so-called hybrid strategy consists of performing LIMA-LAD using off-pump (beating heart) CABG, followed by DES PCI of the remaining stenoses during the same hospitalization (hours or days later, with clopidogrel loading after CABG).
- Occasionally, in patients with critical non-LAD disease, non-LAD disease is stented first, followed by performance of off-pump CABG under clopidogrel therapy.
- The off-pump LIMA-to-LAD surgery offers the advantage of avoiding aortic manipulation, which is necessary during on-pump CABG or during SVG grafting (whether off- or on-pump). Also, the shorter surgical time, the lower blood loss, and the avoidance of cardioplegia and cardiopulmonary bypass are advantages.
- **Currently, the hybrid approach is particularly applicable to:**
Patients with heavily calcified, porcelain aorta in whom aortic manipulation needs to be avoided; Patients with good LAD target but poor LCx and RCA targets that, nonetheless, have severe proximal disease amenable to PCI.

Table 5-11: Aspects to be considered by the Heart Team for decision-making between PCI and CABG among patients with stable multivessel and/or left main coronary artery disease:

| Favours PCI | Favours CABG |
|---|---|
| Clinical characteristics: | |
| <ul style="list-style-type: none"> - Presence of severe co-morbidity (not adequately reflected by scores) - Advanced age/frailty/reduced life expectancy - Restricted mobility and conditions that affect the rehabilitation process | <ul style="list-style-type: none"> - Diabetes - Contraindication to DAPT - Reduced LV function (EF ≤ 35%) - Recurrent diffuse in-stent restenosis |
| Anatomical and technical aspects: | |
| <ul style="list-style-type: none"> - MVD with SYNTAX score 0-22 - Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits | <ul style="list-style-type: none"> - MVD with SYNTAX score ≥ 23 - Anatomy likely resulting in incomplete revascularization with PCI. |

| | |
|---|---|
| <ul style="list-style-type: none"> - Severe chest deformations or scoliosis - Sequelae of chest radiation - Porcelain aorta ⁽¹⁾ | <ul style="list-style-type: none"> - Severely calcified coronary artery lesions limiting lesion expansion. |
| | Need for concomitant cardiac surgery |

(1) Consider no-touch off-pump CABG in case of porcelain aorta.

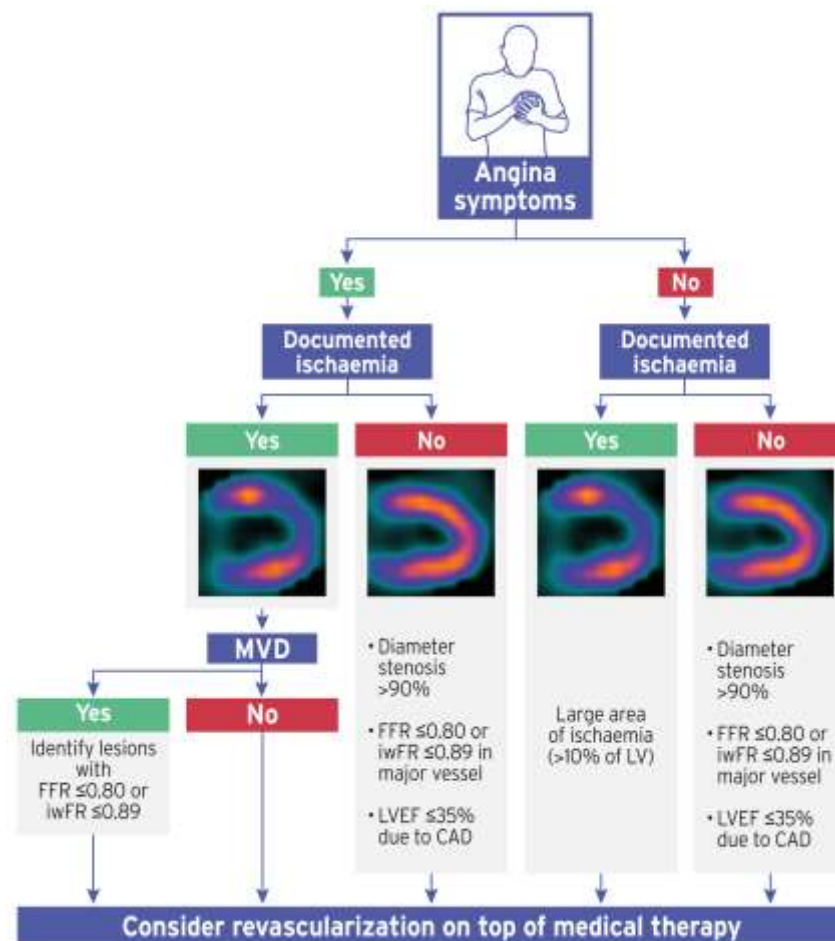


Figure 5-5: Decision tree for patients undergoing invasive coronary angiography. Decisions for revascularization by PCI or CABG are based on clinical presentation (symptoms present or absent), and prior documentation of ischaemia (present or absent). In the absence of prior documentation of ischaemia, indications for revascularization depend on invasive evaluation of stenosis severity or prognostic indications. Patients with no symptoms and ischaemia include candidates for TAVI, or valve surgery. **Source:** 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.

Patients with new onset of heart failure or reduced LV function

CAD is the most common cause of HF in Europe, and most of the trial evidence supporting management recommendations is based on research conducted in patients with ischaemic cardiomyopathy.

Since the STICH trial, it is known that a strategy of CABG added to GDMT compared to medical therapy alone brings a benefit for 10-year survival.

The REVIVED-BCIS2 trial compared PCI to OMT in patients with heart failure with impaired LVEF and advanced CAD with proven viability for at least four myocardial segments. The primary composite outcome was all cause mortality or HF hospitalization. Major secondary outcomes were LVEF at 6 and 12 months and quality-of-life scores. Over a median of 41 months, no difference could be observed between the PCI group and the OMT group with respect to the primary endpoint. The LVEF was similar in the two groups at 6 months and at 12 months. Quality-of-life scores at 6 and 12 months appeared to favour the PCI group, but the difference had diminished at 24 months.

Table 5-12: ESC recommendations for the management of patients with CCS and symptomatic HF due to ischaemic cardiomyopathy and LV systolic dysfunction:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Medical therapy: | | |
| <i>Diuretic therapy is recommended in symptomatic patients with signs of pulmonary or systemic congestion to relieve HF symptoms.</i> | I | B |
| <i>Beta-blockers are recommended as essential components of treatment due to their efficacy in both relieving angina, and reducing morbidity and mortality in HF.</i> | I | A |
| <i>ACEIs therapy is recommended in patients with symptomatic HF <u>or</u> asymptomatic LV dysfunction following MI, to improve symptoms and reduce morbidity and mortality.</i> | I | A |
| <i>An ARB is recommended as an alternative in patients who do not tolerate ACE inhibition, or an ARNI in patients with persistent symptoms despite optimal medical therapy.</i> | I | B |

| | | |
|---|------------|----------|
| <i>An MRA is recommended in patients who remain symptomatic despite adequate treatment with an ACE inhibitor and beta-blocker, to reduce morbidity and mortality.</i> | I | A |
| <i>A short-acting oral or transcutaneous nitrate should be considered (effective antianginal treatment, safe in HF).</i> | IIa | A |
| <i>Ivabradine should be considered in patients with sinus rhythm, an LVEF $\leq 35\%$ and a resting heart rate > 70 b.p.m. who remain symptomatic despite adequate treatment with a beta-blocker, ACE inhibitor, and MRA, to reduce morbidity and mortality.</i> | IIa | B |
| <i>Amlodipine may be considered for relief of angina in patients with HF who do not tolerate beta-blockers, and is considered safe in HF.</i> | IIb | B |
| For devices, comorbidities, and revascularization: | | |
| <i>In patients with HF and bradycardia with high-degree AV block who require pacing, a CRT with a pacemaker rather than RV pacing is recommended.</i> | I | A |
| <i>An ICD is recommended in patients with documented ventricular dysrhythmia causing haemodynamic instability (secondary prevention), as well as in patients with symptomatic HF and an LVEF $\leq 35\%$, to reduce the risk of sudden death and all-cause mortality.</i> | I | A |
| <i>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 ms and LBBB QRS morphology, and with LVEF $\leq 35\%$, despite optimal medical therapy to improve symptoms, and reduce morbidity and mortality.</i> | I | A |
| <i>CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration 130 - 149 ms and LBBB QRS morphology, and with LVEF $\leq 35\%$, despite optimal medical therapy to improve symptoms, and reduce morbidity and mortality.</i> | I | B |
| <i>Myocardial revascularization is recommended when angina persists despite treatment with antianginal drugs.</i> | I | A |

Long-standing diagnosis of chronic coronary syndromes

In patients with a long-standing diagnosis of CCS, lifelong treatment and surveillance are required. The clinical course of patients with CCS may be benign over the course of time. However, patients with CCS may develop a variety of cardiovascular complications or undergo therapeutic measures, some directly related to the underlying CAD, and some having therapeutic or prognostic interactions with the underlying disease. Risk for complications may occur in an otherwise asymptomatic patient, and thus the assessment of risk status applies to symptomatic and asymptomatic patients.

Table 5-13: ESC Recommendations for patients with a long-standing diagnosis of chronic coronary syndromes:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| For asymptomatic patients: | | |
| <i>A periodic visit to a cardiovascular healthcare professional is recommended to reassess any potential change in the risk status of patients, entailing clinical evaluation of lifestyle modification measures, adherence to targets of cardiovascular risk factors, and the development of comorbidities that may affect treatments and outcomes.</i> | I | C |
| <i>In patients with mild or no symptoms receiving medical treatment in whom non-invasive risk stratification indicates a high risk, and for whom revascularization is considered for improvement of prognosis, invasive coronary angiography (with FFR when necessary) is recommended.</i> | I | C |
| <i>Coronary CTA is not recommended as a routine follow-up test for patients with established CAD.</i> | III | C |
| <i>Invasive coronary angiography is not recommended solely for risk stratification.</i> | III | C |
| For Symptomatic patients: | | |
| <i>Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g., long-standing tachycardia or myocarditis).</i> | I | C |

| | | |
|--|----------|----------|
| <i>Risk stratification is recommended in patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG.</i> | I | B |
| <i>It is recommended to expeditiously refer patients with significant worsening of symptoms for evaluation.</i> | I | C |
| <i>Invasive coronary angiography (with FFR/iwFR when necessary) is recommended for risk stratification in patients with severe CAD, particularly if the symptoms are refractory to medical treatment or if they have a high-risk clinical profile.</i> | I | C |

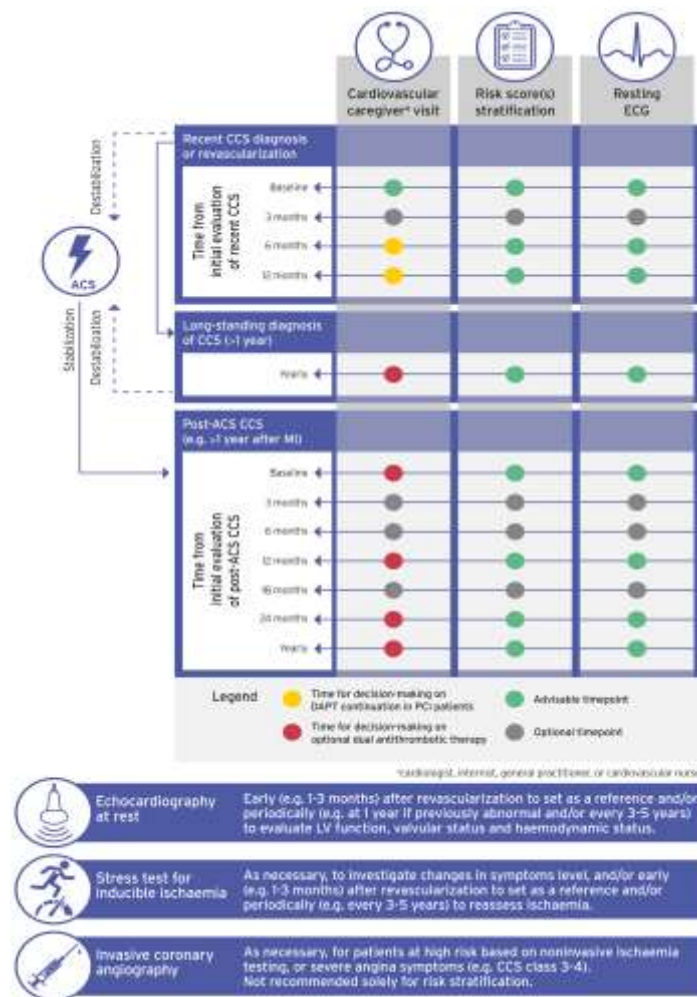


Figure 5-6: Proposed algorithm according to patient types commonly observed at chronic coronary syndrome outpatient clinics. The frequency of follow-up may be subject to variation based on clinical judgement. **A)** Cardiologist, internist, general practitioner, or cardiovascular nurse. **Source:** 2019 ESC Guidelines for the diagnosis and management

Angina with Non obstructive Coronary Artery Disease (ANOCA)

The coronary arterial system consists of epicardial coronary arteries, prearterioles, and arterioles with different sizes, distinct functions, and uninterrupted borders. Myocardial ischemia from the mismatch of demand and supply of coronary artery blood flow to the myocardium can originate from any part of this coronary arterial system. Prearteriolar vessels and arterioles compose the coronary microcirculation.

Aetiology:

Excluding the coronary stenosis of mild or moderate angiographic severity, or diffuse coronary narrowing that might be functionally underestimated by ICA, common causes of symptoms in these patients can be identified either in: **(i)** microcirculatory disorders or **(ii)** dynamic stenosis of the epicardial vessels caused by coronary spasm or intramyocardial bridges, or it may be **(iii)** masked diffuse disease.

- **Microvascular angina:** Microvascular dysfunction has 2 forms, both reflective of endothelial dysfunction:
 - **Structural microvascular disease:** luminal narrowing of microvessels by medial wall or intimal thickening, luminal obstruction caused by thromboembolism, capillary rarefaction, extrinsic vascular compression, and vascular wall infiltration.
 - **Functional microvascular disease:** Impaired capacity to vasodilate to increase flow during exercise. It is known to be associated with endothelium-dependent and/or endothelium-independent mechanisms.
- **Vasospastic angina:** resting chest pain not associated with increased myocardial oxygen demand, chest pain with diurnal variation frequently at night or early morning, and a prompt response to nitroglycerin. Vasospastic angina can also be caused by coronary microvascular spasm, which is associated with the spasm of vascular smooth muscle cells in prearteriolar vessels and arterioles.
- **Masked Diffuse Disease:** Even in INOCA patients, the presence of coronary atherosclerosis is common. Because most of these lesions showed positive remodeling and a preserved lumen size, diffuse coronary atherosclerosis can be unrevealed or

underestimated by coronary angiography. When clinically suspected, the use of intracoronary imaging or invasive physiologic studies can be helpful in diagnosis.

Diagnosis:

Because the diagnosis of INOCA requires both myocardial ischemia and no obstruction in epicardial coronary arteries, defining myocardial ischemia represents the first step in the diagnosis of INOCA.

- **Non-invasive tests for evaluating INOCA:** Because current noninvasive functional tests rely on detecting large regional differences in myocardial perfusion or regional wall motion abnormalities, these tests are hampered in their ability to diagnose coronary microvascular disease.
- **Invasive coronary angiography:** ICA is the current gold standard method for evaluation and treatment planning for obstructive CAD. ICA can provide information on microvascular dysfunction by showing slow coronary flow. However, invasive coronary angiography alone cannot provide objective evidence of microvascular dysfunction or coronary vasospasm. This can be achieved through:
 - **Physiologic tests:** Comprehensive physiologic assessment using a pressure sensor guidewire is needed to discriminate myocardial ischemia caused by epicardial coronary artery lesions and coronary microvascular disease.
 - Fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) is a standard invasive method to define ischemia-causing epicardial coronary artery lesions. $FFR \leq 0.80$ and $iwFR \leq 0.89$ indicate flow-limiting epicardial coronary artery stenosis.
 - After excluding the presence of flow-limiting obstructive coronary artery disease, the assessment of microvascular function is done using coronary flow reserve (CFR). It is an index of how coronary blood flow can be increased during a hyperemic state compared with a resting state, and it is affected by both epicardial coronary artery stenosis and microvascular function. CFR can be measured in cath laboratory using a Doppler wire or a pressure-temperature sensor-equipped guidewire. $CFR \leq 2.0$ or 2.5 indicates the presence of flow-limiting stenosis, microvascular dysfunction, or both.
 - **Provocation test to diagnose vasospastic angina:** If the specific mechanism of INOCA can't be established or if there are specific features of vasospastic angina, a provocation test is needed to diagnose vasospastic angina. The acetylcholine

provocation test and the ergonovine provocation test are the most widely used methods to confirm the presence of coronary artery spasm ⁽¹⁾. When angina and ischemic ECG changes (ST-segment depression or elevation ≥ 0.1 mV) in at least 2 contiguous leads occur after acetylcholine infusion without significant epicardial coronary artery constriction ($< 90\%$), the presence of microvascular spasm can be diagnosed.

| Table 5-14: Diagnosis of ANOCA: | |
|---|---|
| Coronary microvascular disease | Based on invasive physiologic assessment: <ul style="list-style-type: none"> - FFR > 0.80 or iwFR > 0.89 - CFR < 2.0-2.5 - IMR > 25 U or HMR > 2.5 mm Hg/cm/s |
| Epicardial vasospastic angina | Based on provocation test using ergonovine or acetylcholine: <ul style="list-style-type: none"> - Ischemic symptom during provocation test - A transient total or subtotal coronary artery occlusion - Ischemic ECG changes (ST-segment depression or elevation ≥ 0.1 mV) in at least 2 contiguous leads |
| Microvascular vasospastic angina | Based on the provocation test using acetylcholine: <ul style="list-style-type: none"> - Ischemic symptom during provocation test - ST-segment depression or elevation ≥ 0.1 mV in at least 2 contiguous leads without significant epicardial artery constriction during provocation test |
| Masked diffuse disease | Based on invasive physiologic assessment <ul style="list-style-type: none"> - FFR ≤ 0.80 or iwFR ≤ 0.89 with gradual step-up during pull back tracing Based on intravascular imaging studies |

(1) Acetylcholine acts on the muscarinic cholinergic receptors, and ergonovine act on the serotonin receptors in vascular smooth muscle cells.

Management:

To date, there is no standard evidence-based treatment of INOCA because of its heterogeneous mechanisms.

- **Microvascular disease:**

- Optimal management of CV risk factors may prevent the progression of microvascular disease with or without improving microvascular vasodilatory function.
- Aspirin, statin, and ACEIs or ARBs were considered as a baseline therapy, and a beta-blocker was considered as first-line therapy and a CCB as second-line therapy for anti-anginal effects.

- **Vasospastic angina:**

- CCBs and nitrates, are the most important treatment options for vasospastic angina. Non-DHB CCBs are preferred in vasospastic angina, but dihydropyridine CCBs also can be used.
- In patients with refractory symptoms, nicorandil, alpha-1 receptor blockers, or Rho-kinase inhibitors can be additional options for vasospastic angina.
- To prevent angina in the early morning or at midnight, medication before sleep can be useful to prevent the symptom.
- For patients with vasospastic angina, the use of beta-blockers, both selective or nonselective, should be avoided because of the possible effects on smooth muscle vasospasm with blocking beta-2 receptors.

| Table 5-15: ESC recommendations for Diagnostic workup in patients with ANOCA: | | |
|--|------------|----------|
| Recommendations | Class | Level |
| Diagnosis of suspected coronary microvascular angina: | | |
| <i>Guidewire-based Coronary flow reserve and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm.</i> | IIb | B |
| <i>Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR.</i> | IIb | B |
| Diagnosis of suspected vasospastic angina: | | |
| <i>An ECG is recommended during angina if possible.</i> | I | C |
| <i>Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.</i> | IIa | C |
| <i>Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease.</i> | I | C |
| <i>An intracoronary provocation test should be considered to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm.</i> | IIa | B |

Refractory angina

Refractory angina refers to long-lasting symptoms (for ≥ 3 months) due to established reversible ischaemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting including PCI of CTO lesions.

- **Enhanced external counterpulsation (EECP):** This therapy consists of inflating cuffs around the lower extremities during diastole, and deflating them in systole, creating an effect similar to IABP. The systolic cuff depression reduces LV afterload and O₂ demands. It may also have a sustained effect on endothelial function, collateral function, and oxidative stress, explaining the sustained benefit. EECP consists of 35 one-hour sessions.
- **Reducer device for coronary sinus constriction:** An endoluminal, balloon-expandable, stainless steel, hourglass-shaped device designed for percutaneous implantation in the coronary sinus creates a focal narrowing that leads to increased pressure in the coronary sinus, thus redistributing blood into ischemic myocardium which may relieve angina.
- **Spinal cord stimulation** is a treatment option that has been developed for patients with refractory angina. Four possible mechanisms explaining the beneficial effects of SCS on RAP have been described: reduction of pain perception, decreased sympathetic tone, reduced myocardial oxygen demand and improved coronary microcirculatory blood flow.

Table 5-16: ESC Recommendations for treatment options for refractory angina:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Enhanced external counterpulsation may be considered for symptom relief in patients with debilitating angina refractory to optimal medical and revascularization strategies.</i> | IIb | B |
| <i>A reducer device for coronary sinus constriction may be considered to ameliorate symptoms of debilitating angina refractory to optimal medical and revascularization strategies.</i> | IIb | B |

| | | |
|--|------------|----------|
| <i>Spinal cord stimulation may be considered to ameliorate symptoms and quality of life in patients with debilitating angina refractory to optimal medical and revascularization strategies.</i> | IIb | B |
| <i>Transmyocardial revascularization is not recommended in patients with debilitating angina refractory to optimal medical and revascularization strategies.</i> | III | A |

Screening for coronary artery disease in asymptomatic subjects:

| Table 5-17: ESC Recommendations for screening for coronary artery disease in asymptomatic subjects | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults > 40 years of age without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia.</i> | I | C |
| <i>Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event, or/and established diagnosis of CVD in first-degree male relatives before 55 years of age or female relatives before 65 years of age) is recommended as part of cardiovascular risk assessment.</i> | I | C |
| <i>It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolaemia are screened using a validated clinical score.</i> | I | B |
| <i>Assessment of coronary artery calcium score with computed tomography may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects.</i> | IIb | B |

| | | |
|--|------------|----------|
| <i>Atherosclerotic plaque detection by carotid artery ultrasound may be considered as a risk modifier in the cardiovascular risk assessment of asymptomatic subjects.</i> | IIb | B |
| <i>ABI may be considered as a risk modifier in cardiovascular risk assessment.</i> | IIb | B |
| <i>In high-risk asymptomatic adults (with diabetes, a strong family history of CAD, or when previous risk-assessment tests suggest a high risk of CAD), functional imaging or coronary CTA may be considered for cardiovascular risk assessment.</i> | IIb | C |
| <i>In asymptomatic adults (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for cardiovascular risk assessment, particularly when attention is paid to non-ECG markers such as exercise capacity.</i> | IIb | C |
| <i>Carotid ultrasound IMT for cardiovascular risk assessment is not recommended.</i> | III | A |
| <i>In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia are not indicated for further diagnostic assessment.</i> | III | C |
| <i>Routine assessment of circulating biomarkers is not recommended for cardiovascular risk stratification.</i> | III | B |

Chronic coronary syndromes in specific circumstances:

Table 5-18: ESC recommendations for Management of Chronic coronary syndromes in specific circumstances:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Hypertension: | | |
| <i>It is recommended that office BP is controlled to target values: systolic BP 120 - 130 mmHg in general and systolic BP 130 - 140 mmHg in older patients (aged >65 years).</i> | I | A |

| | | |
|---|------------|----------|
| <i>In hypertensive patients with a recent MI, beta blockers and RAS blockers are recommended.</i> | I | A |
| <i>In patients with symptomatic angina, beta blockers and/or CCBs are recommended.</i> | I | A |
| <i>The combination of ACE inhibitors and ARBs is not recommended.</i> | III | A |
| Valvular heart disease: | | |
| <i>ICA is recommended before valve surgery and for any of the following: history of CVD, suspected myocardial ischaemia, LV systolic dysfunction, in men >40 years of age and post menopausal women, or one or more cardiovascular risk factors.</i> | I | C |
| <i>ICA is recommended in the evaluation of moderate-to-severe functional mitral regurgitation.</i> | I | C |
| <i>Coronary CTA should be considered as an alternative to coronary angiography before valve intervention in patients with severe valvular heart disease and low probability of CAD.</i> | Ila | C |
| <i>PCI should be considered in patients undergoing transcatheter aortic valve implantation and coronary artery diameter stenosis >70% in proximal segments.</i> | Ila | C |
| <i>In severe valvular heart disease, stress testing should not be routinely used to detect CAD because of the low diagnostic yield and potential risks.</i> | III | C |
| Diabetes Mellitus: | | |
| <i>Risk factor (BP, LDL-C, and HbA1c) control to targets is recommended in patients with CAD and diabetes mellitus.</i> | I | A |
| <i>In asymptomatic patients with diabetes mellitus, a periodic resting ECG is recommended for cardiovascular detection of conduction abnormalities, AF, and silent MI.</i> | I | C |

| | | |
|---|------------|----------|
| <i>ACE inhibitor treatment is recommended in CCS patients with diabetes for event prevention.</i> | I | B |
| <i>The sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD.</i> | I | A |
| <i>A glucagon-like peptide-1 receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes and CVD.</i> | I | A |
| <i>In asymptomatic adults (age >40 years) with diabetes, functional imaging or coronary CTA may be considered for advanced cardiovascular risk assessment.</i> | IIb | B |
| Chronic Kidney disease: | | |
| <i>It is recommended that risk factors are controlled to target values.</i> | I | A |
| <i>It is recommended that special attention is paid to potential dose adjustments of renally excreted drugs used in CCS.</i> | I | C |
| <i>It is recommended that the use of iodinated contrast agents is minimized in patients with severe CKD and preserved urine production to prevent further deterioration.</i> | I | B |
| Cancer: | | |
| <i>Treatment decisions should be based on life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis propensity, and potential interactions between drugs used in CCS management and antineoplastic agents.</i> | I | C |
| <i>If revascularization is indicated in highly symptomatic patients with active cancer and increased frailty, the least invasive procedure is recommended.</i> | I | C |
| Elderly patients: | | |
| <i>It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients.</i> | I | C |

| | | |
|---|------------|----------|
| <i>The use of DES is recommended in elderly patients.</i> | I | A |
| <i>Radial access is recommended in elderly patients to reduce access-site bleeding complications.</i> | I | B |
| <i>It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities.</i> | I | C |
| Sex issues: | | |
| <i>Hormone replacement therapy is not recommended for risk reduction in post-menopausal women.</i> | III | C |

After heart transplantation:

ICA is recommended for the assessment of transplant CAD and should be performed annually for 5 years after transplantation.

Comparison between 2023 ACC and 2019 ESC guidelines in CCS:

Table 5-19: Comparison between 2023 ACC and 2019 ESC guidelines in CCS:

| 2023 ACC for the Management of Chronic Coronary Disease | | 2019 ESC Guidelines for the Management of Chronic Coronary Syndromes | |
|---|-------|--|-----|
| SGLT2-i: | | | |
| In patients with CCD who have type 2 diabetes, the use of either an SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefit is recommended to reduce the risk of MACE | I-A | The SGLT2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD. | I-A |
| In patients with CCD and HF with LVEF ≤40%, use of an SGLT2 inhibitor is recommended to reduce the risk of cardiovascular death and HF hospitalisation and to improve QOL, irrespective of diabetes status. | I-A | | |
| In patients with CCD and HF with LVEF >40%, use of an SGLT2 inhibitor can be beneficial in decreasing HF hospitalisations and to improve QOL irrespective of diabetes status. | Ila-B | | |
| Beta-blockers: | | | |

| | | | |
|---|--------------|---|--------------|
| In patients with CCD and LVEF $\leq 40\%$ with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death | I-A | Beta-blockers are recommended in patients with LV dysfunction or systolic HF. | I-A |
| In patients with CCD and LVEF $< 50\%$, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta-blockers. | I-A | Beta-blockers are recommended as essential components of treatment due to their efficacy in both relieving angina and reducing morbidity and mortality in HF. | I-A |
| In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF $\leq 50\%$, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. | IIb-B | In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered. | IIa-B |
| In patients with CCD without previous MI or LVEF $\leq 50\%$, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. | III-B | No corresponding recommendation | |

Antianginal therapy:

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|--|--------------|---|--------------|
| In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. | I-B | First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms | I-A |
| In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. | I-B | If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered. | IIa-C |
| In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta-blockers, CCB, or long-acting nitrate therapies. | I-B | Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms | IIa-B |
| | | Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates | IIa-B |
| In patients with CCD and normal LV function, the addition of ivabradine to standard antianginal therapy is potentially harmful. | III-B | In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance. | IIb-C |

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| | | In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance. | IIb-B |
| Lipid-lowering therapy: | | | |

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|---|--------------|--|------------|
| In patients with CCD, high-intensity statin therapy is recommended with the aim of achieving a >50% reduction in LDL-C levels to reduce the risk of MACE | I-A | Statins are recommended in all patients with CCS. | I-A |
| In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥ 70 mg/dL (≥ 1.8 mmol/L), ezetimibe can be beneficial to further reduce the risk of MACE. | IIa-B | If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. | I-B |
| In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥ 70 mg/dL (≥ 1.8 mmol/L), or a non-HDL-C level ≥ 100 mg/dL (≥ 2.6 mmol/L), on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE | IIa-A | For patients at very high risk who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended. | I-A |
| In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥ 70 mg/dL (≥ 1.8 mmol/L), and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. | IIb-B | No corresponding recommendation. | |
| Antithrombotic therapy: | | | |

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| In patients with CCD and no indication for oral anticoagulant therapy, low- dose aspirin 81 mg (75-100 mg) is recommended to reduce atherosclerotic events | I-A | Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularisation. | I-A |
| | | Aspirin 75-100 mg daily is recommended following stenting. | I-A |
| In patients with CCD treated with PCI, DAPT consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy is indicated to reduce MACE and bleeding events | I-A | Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1-3 months) is indicated due to risk or the occurrence of life-threatening bleeding. | I-A |
| In selected patients with CCD treated with PCI and a drug-eluting stent who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk | Ila-A | Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding. | Ila-A |
| | | Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding. | Ilb-C |

Important trials in chronic coronary syndrome:

| Table 5-20: Clinical trials of Stable Coronary artery disease: | |
|--|--|
| Trial (date) | Summary |
| ACEIs & ARBs: | |
| HOPE (2000) | <p>Aim: to assess the efficacy of ACEI or vitamin E on morbidity and mortality in patients at high risk of CV events compared with placebo.</p> <p>Study: 9297 patients at high risk of CV events who are not known to have a low EF or HF were randomized to ramipril (10 mg/day) or placebo. In a factorial design, patients were also randomized to vitamin E or placebo. Ramipril significantly reduces the rates of death, MI, and stroke.</p> |
| ONTARGET (2008) | <p>Aim: to determine whether the telmisartan (ARB) was noninferior to ramipril (ACEI), and whether a combination of the two drugs was superior to ramipril alone as a treatment to prevent vascular events in high-risk patients who had CV disease or DM, but did not have HF.</p> <p>Study: 25620 patients in high-risk patients with CV disease or DM, without overt congestive HF were randomized in a 1:1:1 pattern to receive either 80 mg of telmisartan daily, 5 mg of ramipril daily, or combination therapy at the same doses. After 2 weeks, the dose of ramipril was increased to 10 mg daily. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.</p> |
| Lipid Lowering therapy: | |
| 4S (1994) | <p>Aim: To evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary artery disease.</p> <p>Study: 4444 patients with angina pectoris or previous MI and serum cholesterol 220-320 mg/dl (5.5-8.0 mmol/L) on a lipid-lowering diet were randomised to simvastatin or placebo. Long-term treatment with simvastatin is safe and improves survival in patients with coronary artery disease.</p> |

| | |
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| SATURN (2011) | <p>Aim: To compare treatment with rosuvastatin with atorvastatin among patients with symptomatic coronary artery disease.</p> <p>Study: 1039 patients 18-75 years of age with symptomatic coronary artery disease (> 20% stenosis) and LDL-C > 80 mg/dl on statin therapy, or > 100 mg/dl not on statin therapy were randomized again to rosuvastatin (40 mg daily) versus atorvastatin (80 mg daily). Study drugs were administered for 2 years. Patients had an IVUS at baseline and again at follow-up. The primary endpoint was significant regression of coronary atherosclerosis assessed with percent atheroma volume (PAV). Despite the lower level of LDL-C and the higher level of HDL-C achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups.</p> |
| AIM-HIGH (2011) | <p>Aim: To determine whether raising HDL-C with niacin, while lowering LDL-C with statin, can prevent more heart disease than the statin alone.</p> <p>Study: 3414 patients with atherosclerotic CV disease and LDL-C < 70 mg/dl were randomly assigned to receive extended-release niacin (1500 to 2000 mg/day) or matching placebo. All patients received simvastatin (40 to 80 mg/day) plus ezetimibe (10 mg/day), if needed, to maintain an LDL-C of 40 to 80 mg/dl. There was no incremental clinical benefit from the addition of niacin to statin during a 36-month follow-up period, despite significant improvements in HDL-C and triglyceride levels.</p> |
| Anti-inflammatory drugs: | |
| LoDoCo2 (2020) | <p>Aim: To determine whether 0.5 mg of colchicine once daily prevents CV events in patients with chronic coronary disease.</p> <p>Study: 5522 patients with chronic coronary disease were randomly assigned to receive 0.5 mg of colchicine once daily or matching placebo. The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.</p> |
| Coronary revascularization: | |

CABG vs. OMT:

Since the STICH trial, it is known that a strategy of CABG added to GDMT brings a benefit for 10-year survival, as compared to medical therapy alone.

STICH (2011)

Aim: *To assess the role of CABG in the treatment of patients with coronary artery disease and heart failure.*

Study: *1212 patients with LVEF \leq 35% and coronary artery disease amenable to CABG were randomly assigned to medical therapy alone or medical therapy plus CABG. The primary outcome was the rate of death from any cause. The rates of all-cause mortality, CV mortality, and hospitalization for CV causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone.*

PCI vs. OMT:

- *Among patients with stable CAD, COURAGE and BARI 2D trials failed to demonstrate any significant benefit from coronary revascularization compared to OMT in the occurrence of all-cause death or CV outcomes. One of the criticisms of these trials was the possibility that all patients with most severe CAD involvement that might be associated with a very high risk for adverse ischemic outcomes were likely not randomized but sent directly to invasive revascularization.*
- *To avoid this major selection bias, the ISCHEMIA trial randomized patients before coronary angiogram. In line with historical trials, the ISCHEMIA trial did not find evidence that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of ischemic CV events or death from any cause over a median of 3.2 years in 5179 patients with documented moderate or severe ischemia on stress tests. For this trial there were also several limitations to note. (i) most patients included were asymptomatic or only mildly symptomatic at baseline, when it is precisely the effect of revascularization on effective angina relief that is expected. (ii) all participants were screened before randomization with a coronary CT angiography and were excluded from the ISCHEMIA trial in case of left main stenosis of at least 50%.*
- *The REVIVED-BCIS2 trial compared PCI to OMT in patients with heart failure with impaired LVEF and advanced CAD with proven viability for at least four myocardial segments. Over a median of 41 months, no difference could be observed between the PCI group and the OMT group with respect to the primary endpoints (all-cause mortality or HF hospitalization). The LVEF*

was similar in the two groups at 6 months and at 12 months. Quality-of-life scores at 6 and 12 months appeared to favour the PCI group, but the difference had diminished at 24 months.

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| COURAGE (2007) | <p>Aim: <i>To evaluate the efficacy of PCI compared with optimal medical therapy among patients with stable coronary artery disease.</i></p> <p>Study: <i>2287 patients who had objective evidence of myocardial ischemia, significant CAD, and LVEF \geq 30% were randomly assigned to undergo PCI with optimal medical therapy and to receive optimal medical therapy alone. As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, MI, or other major CV events when added to optimal medical therapy.</i></p> |
| BARI-2D (2009) | <p>Aim: <i>To determine whether early revascularization compared with medical therapy in these patients reduces mortality and morbidity. It is also designed to determine whether treatment targeted to attenuate insulin resistance can retard progression of CAD compared with treatment with an insulin-providing approach.</i></p> <p>Study: <i>2368 patients with both type 2 DM and heart disease were randomly assigned to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy. Primary end points were the rate of death and a composite of major cardiovascular events. There was no significant difference in the rates of MACE between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision.</i></p> |
| FAME-2 (2012) | <p>Aim: <i>To study if there would be a difference in outcomes after FFR-guided PCI with OMT versus OMT alone in patients with stable angina.</i></p> <p>Study: <i>1220 patients with LVEF \geq 30% in whom at least one stenosis was functionally significant (FFR \leq 0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). The primary end point was a composite of death, MI,</i></p> |

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| | <i>or urgent revascularization. FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization.</i> |
| ISCHEMIA (2019) | <p>Aim: <i>To evaluate routine invasive therapy compared with optimal medical therapy among patients with stable ischemic heart disease and moderate to severe myocardial ischemia on noninvasive stress testing.</i></p> <p>Study: <i>5179 patients with moderate or severe ischemia and LVEF \geq 35% were randomly assigned to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial medical therapy alone and angiography if medical therapy failed. The primary outcome was a composite of CV mortality, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Invasive strategy, as compared with conservative strategy, did not reduce the risk of ischemic CV events or death from any cause over median of 3.2 years.</i></p> |
| REVIVED-BCIS2 (2022) | <p>Aim: <i>To evaluate PCI compared with optimal medical therapy among individuals with LVEF \leq 35% and extensive CAD.</i></p> <p>Study: <i>700 patients with a LVEF \leq 35%, extensive coronary artery disease amenable to PCI, and demonstrable myocardial viability were randomly assigned to either PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone (optimal-medical-therapy group). The primary composite outcome was all cause mortality or HF hospitalization. Among patients with LV systolic dysfunction and extensive CAD, multivessel PCI did not improve all-cause mortality or LV systolic function; however, there was no harm from this approach. Scar burden, but not viability characteristics at baseline, predicts likelihood of LV recovery. It remains possible that patients with the most severe CAD were referred for CABG.</i></p> |
| CABG vs. PCI in LM and multivessel disease: | |
| <p>CABG vs. PCI in multi-vessel disease:</p> <p><i>Patients with complex three-vessel coronary artery disease have been found to have better outcomes with CABG than with PCI, especially in the case of DM. When coronary lesions are less extensive (defined by a SYNTAX score \leq 22), PCI is recommended equally to CABG in non-diabetic patients. However, trials have rarely used second-generation DES and have not routinely</i></p> | |

measured FFR to guide PCI. The FAME 3 trial was a multicentre, noninferiority trial randomly assigned 1500 patients with three-vessel coronary artery disease to undergo CABG or FFR-guided PCI. FFR-guided PCI was not found to be noninferior to CABG with respect to the incidence of a composite of death, MI, stroke, or repeat revascularization at 1 year.

CABG vs. PCI in left main disease:

Several RCTs comparing PCI using early-generation DES with CABG for treating LMCA disease have suggested comparable clinical outcomes of PCI and CABG (SYNTAX-LM and PRECOMBAT trials). Recently, 2 landmark RCTs (EXCEL and NOBLE) were sufficiently powered to determine the clinical effectiveness of PCI with contemporary DES compared to standard CABG for LMCA disease. However, these 2 landmark RCTs showed somewhat conflicting results; EXCEL found that PCI was noninferior to CABG, whereas NOBLE failed to show noninferiority for PCI compared with CABG. Based on the currently available totality of the evidence, CABG and PCI with DES for the treatment of LMCA disease have comparable risks for overall mortality and the composite of death, MI, or stroke up to 5 to 10 years of follow-up. The risks of procedural MI and stroke were greater with CABG, whereas the risk of spontaneous MI was greater with PCI.

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|--------------------------|---|
| BARI (2007) | <p>Aim: To compare 10-year clinical outcomes in patients who were randomly assigned to PTCA versus CABG.</p> <p>Study: 1829 Symptomatic patients with multivessel CAD were randomly assigned to initial treatment with PTCA or CABG and followed up for an average of 10.4 years. There was no significant long-term disadvantage regarding mortality or MI associated with an initial strategy of PTCA compared with CABG. Among patients with treated diabetes, CABG conferred long-term survival benefit, whereas the 2 initial strategies were equivalent regarding survival for patients without diabetes.</p> |
| SYNTAX (2009) | <p>Aim: To compare PCI and CABG for treating patients with previously untreated three-vessel or left main coronary artery disease (or both).</p> <p>Study: 1800 patients with three-vessel or left main coronary artery disease were randomly assigned to undergo CABG or PCI. For all these patients, the local cardiac surgeon and interventional cardiologist determined that equivalent anatomical revascularization could be achieved with either treatment. Primary endpoints were MACCE (all-cause mortality, stroke, MI, or repeat revascularization) at 1, 3, 5, and 10 years. CABG, as compared</p> |

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| | <p><i>with PCI, resulted in lower rates of the combined end point of MACCE at 1 year which were predominantly driven by the need for repeat revascularization in the PCI arm. CABG is, however, associated with a higher risk of CVA at 12 months. Importantly, there is no difference in the incidence of death, MI, or graft occlusion/stent thrombosis between the two arms. The largest benefit from CABG seems to be in patients with DM.</i></p> |
| FREEDOM (2012) | <p>Aim: <i>To assess if medical therapy and the use of DES could alter the revascularization approach for patients with DM and multivessel CAD.</i></p> <p>Study: <i>1900 patients with diabetes and multivessel CAD were randomly assigned to undergo either PCI with DESs or CABG. The patients were followed for a minimum of 2 years. For patients with diabetes and advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and MI, with a higher rate of stroke.</i></p> |
| FAME 3 (2022) | <p>Aim: <i>To demonstrate the noninferiority of FFR-guided PCI to CABG for patients with three-vessel disease.</i></p> <p>Study: <i>1500 patients with angiographic stenosis $\geq 50\%$ in three major epicardial vessels without left main involvement who are amenable to revascularization by both PCI and CABG were randomized to either FFR-guided PCI or CABG. In the PCI arm, all lesions with FFR value ≤ 0.80 were stented with current-generation DES. All patients were preloaded with P2Y12 inhibitors and high-dose statin. Post-PCI FFR measurement was recommended. DAPT was continued for at least 6 months. In patients with three-vessel coronary artery disease, FFR-guided PCI was not found to be noninferior to CABG with respect to the incidence of a composite of death, MI, stroke, or repeat revascularization at 1 year.</i></p> |
| PRECOMBAT (2011) | <p>Aim: <i>To determine whether the outcomes after PCI are similar to those after CABG in patients with unprotected left main coronary artery disease.</i></p> <p>Study: <i>600 patients with unprotected left main coronary artery stenosis were randomly assigned to undergo CABG or PCI with sirolimus-eluting stents. The primary composite end point of major adverse cardiac or cerebrovascular events (death from any cause, MI, stroke, or ischemia-driven target-vessel revascularization) at 1 year. PCI with sirolimus-eluting stents was shown to be noninferior to CABG with respect to MACE. However, the noninferiority margin was wide, and the results cannot be considered clinically directive.</i></p> |

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| EXCEL (2019) | <p>Aim: <i>To compare outcomes following CABG and PCI with second-generation DES in patients with unprotected left main disease.</i></p> <p>Study: <i>1905 patients with left main coronary artery disease of low or intermediate anatomical complexity were randomly assigned to undergo either PCI with fluoropolymer-based cobalt–chromium everolimus-eluting stents or CABG. The primary outcome was a composite of death, stroke, or MI. In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or MI at 5 years.</i></p> |
| NOBLE (2019) | <p>Aim: <i>To compare outcomes following CABG and PCI with DES (88% biolimus) in patients with unprotected left main disease.</i></p> <p>Study: <i>1201 patients with left main CAD requiring revascularisation were randomly assigned to receive PCI or CABG. The primary endpoint was major adverse cardiac or cerebrovascular events (MACCE), a composite of all-cause mortality, non-procedural MI, repeat revascularisation, and stroke. In revascularisation of left main CAD, PCI was associated with an inferior clinical outcome at 5 years compared with CABG. Mortality was similar after the two procedures, but patients treated with PCI had higher rates of non-procedural MI and repeat revascularisation.</i></p> |

Refrences and suggested readings:

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Chapter 6:

Universal Definition of Myocardial Infarction

Acute coronary syndromes (ACS) encompass a spectrum of conditions that include patients presenting with recent changes in clinical symptoms or signs, with or without changes on 12-lead ECG and with or without acute elevations in cardiac troponin (cTn). Patients presenting with suspected ACS may eventually receive a diagnosis of acute MI or unstable angina (UA). The diagnosis of MI is made based on the fourth universal definition of MI.

Table 6-1: Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury:

Detection of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values ⁽¹⁾.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI):

The term acute myocardial infarction should be used when there is: **(i)** acute myocardial injury (rise and/or fall of cTn values with at least one value above the 99th percentile URL) with **(ii)** clinical evidence of acute myocardial ischaemia (detection of at least one of the following):

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

(1) Isolated myocardial necrosis is common in critically ill patients and manifests as a troponin rise, sometimes with a rise and fall pattern, but no clinical or ECG features of MI. This troponin rise is not called MI but is called “non-MI troponin elevation” or “**non- ischemic myocardial injury**”.

Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy meets criteria for type 1 MI.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed type 4a MI.

Coronary artery bypass grafting (CABG) related MI is termed type 5 MI.

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values.

Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable ($\leq 20\%$ variation) or falling, must meet the criteria for a > 5 or > 10 -fold increase and manifest a change from the baseline value of $> 20\%$.

In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to type 4a MI only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria.

Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction:

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

Pathology of myocardial ischaemia and infarction:

MI is defined pathologically as myocardial cell death due to prolonged ischaemia.

Diminished cellular glycogen, relaxed myofibrils, mitochondrial abnormalities and sarcolemmal disruption, are the first ultrastructural changes and are seen as early as 10–15 min after the onset of ischaemia.

It can take hours before myocyte necrosis can be identified by postmortem examination in humans; this is in contrast to animal models, in which biochemical evidence of myocardial cell death due to apoptosis can be detected within 10 min of induced myocardial ischaemia in association with myocyte death.

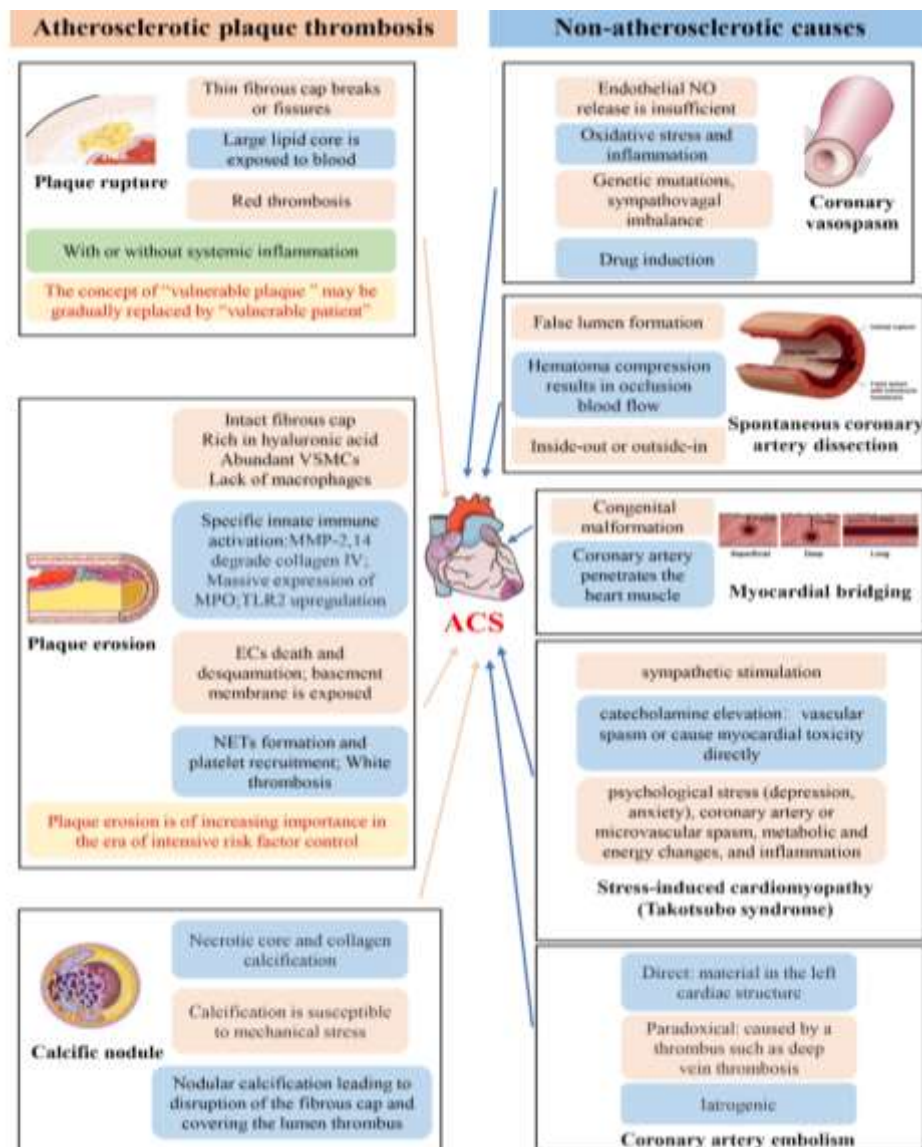


Figure 6-1: Schematic representation of the pathophysiological mechanism of ACS. MMP, metalloproteinases; ECs, endothelial cells; TLR2, Toll-like receptor-2; NETs, neutrophil extracellular traps; MPO, myeloperoxidase. **Source:** Yuan D, Chu J, Qian J, et al. New Concepts on the Pathophysiology of Acute Coronary Syndrome. Reviews in Cardiovascular Medicine. 2023 Apr 17;24(4):112.

Biomarker detection of myocardial injury and infarction:

- **Cardiac troponin I (cTnI) and T (cTnT)** are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart ⁽¹⁾. cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury, and high-sensitivity (hs)-cTn assays are recommended for routine clinical use. Troponin rises above MI cutoff within 3 hours of an episode of ischemia lasting > 20-30 min. Hs-troponin rises above detection cutoff rapidly, usually within 1 hour of ischemia. Other biomarkers, e.g. **creatinine kinase MB isoform (CK-MB)**, are less sensitive and less specific. Overall, CK-MB testing is not recommended on a routine basis but has one potential application: in patients with marked troponin elevation and subacute symptom onset, CK-MB helps diagnose the age of the infarct (a normal CK-MB implies that MI is several days old).
- **Myocardial injury** is present when blood levels of cTn are increased above the 99th percentile URL. The injury may be acute (as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL), **or** chronic (in the setting of persistently elevated cTn levels).
- **Causes of troponin elevation:** Although elevated cTn values reflect injury to myocardial cells, they do not indicate the underlying pathophysiological mechanisms, and can arise following preload-induced mechanical stretch or physiological stresses in otherwise normal hearts. Various mechanisms have been suggested for the release of structural proteins from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs, and myocyte necrosis. Yet, it is not clinically possible to distinguish which increases of cTn levels are due to which mechanisms. However, regardless of the mechanism, acute myocardial injury, when associated with a rising and/or falling pattern of cTn values with at least one value above the 99th percentile URL and caused by myocardial ischaemia, is designated as an acute MI. Myocardial ischaemic or non-ischaemic condition associated with increased cTn values are presented in Table below.

Table 6-2: Reasons for the elevation of cardiac troponin because of myocardial injury:

Myocardial injury related to acute myocardial ischaemia:

(1) Whereas troponin I and T are also present in skeletal muscles, the muscular configuration is different and is not detected by the cardiac troponin assays.

Atherosclerotic plaque disruption with thrombosis.

Myocardial injury related to acute oxygen supply/demand imbalance:

Reduced myocardial perfusion, e.g:

- *Coronary artery spasm, microvascular dysfunction*
- *Coronary embolism*
- *Coronary artery dissection*
- *Sustained bradyarrhythmia*
- *Hypotension or shock*
- *Respiratory failure*
- *Severe anaemia*

Increased myocardial oxygen demand, e.g.

- *Sustained tachyarrhythmia*
- *Severe hypertension with or without LVH.*

Other causes of myocardial injury:

Cardiac conditions, e.g.

- *Heart failure*
- *Myocarditis*
- *Cardiomyopathy (any type)*
- *Takotsubo syndrome*
- *Coronary revascularization procedure*
- *Cardiac procedure other than revascularization*
- *Catheter ablation*
- *Defibrillator shocks*
- *Cardiac contusion*

Systemic conditions, e.g.

- *Critical illness (e.g. Sepsis, infectious disease)*
- *Chronic kidney disease.*
- *Stroke, subarachnoid haemorrhage*
- *Pulmonary embolism, pulmonary hypertension*
- *Infiltrative diseases, e.g. amyloidosis, sarcoidosis*
- *Chemotherapeutic agents*
- *Rhabdomyolysis*
- *Strenuous exercise*

- Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)

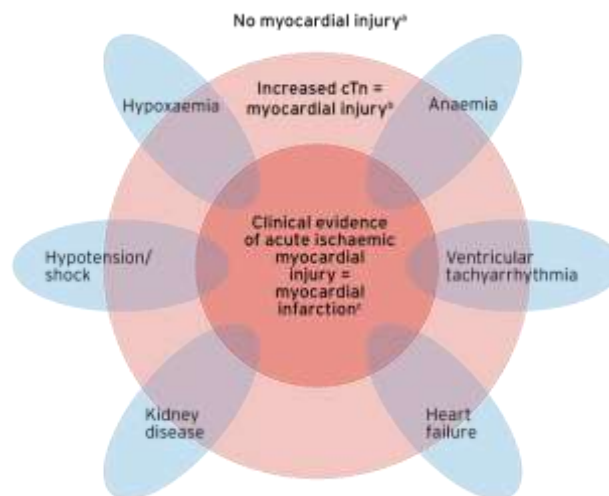


Figure 6-2: Spectrum of myocardial injury, ranging from no injury to myocardial infarction. Various clinical entities may involve these myocardial categories, e.g. ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, hypoxemia, and anaemia. **A)** No myocardial injury = cTn values \leq 99th percentile URL or not detectable. **B)** Myocardial injury = cTn values $>$ 99th percentile URL. **C)** Myocardial infarction = clinical evidence of myocardial ischaemia and a rise and/or fall of cTn values $>$ 99th percentile URL. **Source:** Fourth universal definition of myocardial infarction (2018)

- **Kinetics of troponin rise and decline:**

Detection of a rise and/or fall of cTn values is essential, and a key early component along with other elements of the clinical evaluation to establish the diagnosis of acute MI.

In MI, troponin peaks at 18-24 hours and remains elevated for 7-14 days. However, in small MI, troponin usually normalizes within 2–3 days. In acutely reperfused infarcts (STEMI or NSTEMI), those markers peak earlier (e.g., 12 -18 hours) and

sometimes peak to higher values than if not reperfused, but decline faster. Hence, the total amount of biomarkers released (meaning the area under the curve), is rather than the actual biomarker peak, correlates with the infarct size.

It should be appreciated that because biomarker release is substantially dependent on blood flow, there is significant variability in the time to peak value, the time when a normal value may become greater than the 99th percentile URL, or when a changing pattern of values can be observed. The ability to define a changing pattern will also depend on timing. For example, around peak values, it may be difficult to observe a changing pattern of values. Similarly, the downslope of the time–concentration curve is much slower than the upslope ⁽¹⁾. These issues need to be taken into account when defining whether or not a changing pattern is present.

(1) *Thus, patients presenting late after an infarct may have a plateau pattern of stable troponin.*

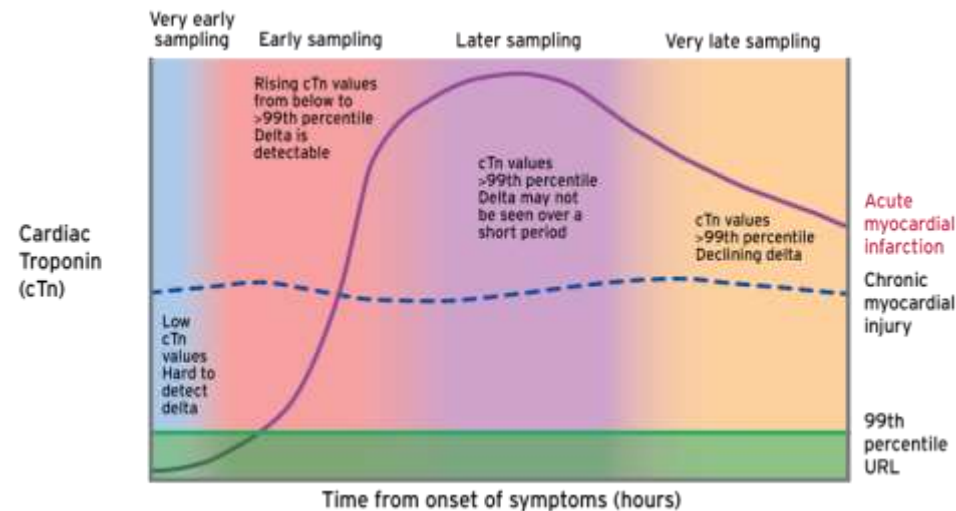


Figure 6-3: Illustration of early cardiac troponin kinetics in patients after acute myocardial injury including AMI. The timing of biomarker release into the circulation is dependent on blood flow and how soon after the onset of symptoms samples are obtained. Thus, the ability to consider small changes as diagnostic can be problematic. In addition, many comorbidities increase cTn values and, in particular, hs-cTn values, so that elevations can be present at baseline even in those with myocardial infarction who present early after the onset of symptoms. Changes in cTn values or deltas can be used to define acute compared with chronic events, and the ability to detect these is indicated in the figure. Increased cTn values can often be detected for days after an acute event. **Source:** Fourth universal definition of myocardial infarction (2018).

- **Analytical issues of cardiac troponins:**

Troponin assays includes: hs-cTn, contemporary (conventional) cTn, or point of care (POC) cTn. While hs-cTn assays are able to measure relatively low values and document small increases above the 99th percentile URL, many contemporary and POC cTn assays may not detect small increasing values within the reference interval or slightly above the 99th percentile URL, leading to substantial differences in the frequency of events based solely on the cTn assay used.

It is recommended that values for cTn assays be reported as whole numbers in (ng/L) to avoid interpretation problems associated with multiple zeros and decimal points that can result in confusion.

All assays, including cTn, have some analytical problems resulting in false positive and false negative results, but these are uncommon (< 0.5%) ⁽¹⁾. These problems are less common with hs-cTn assays.

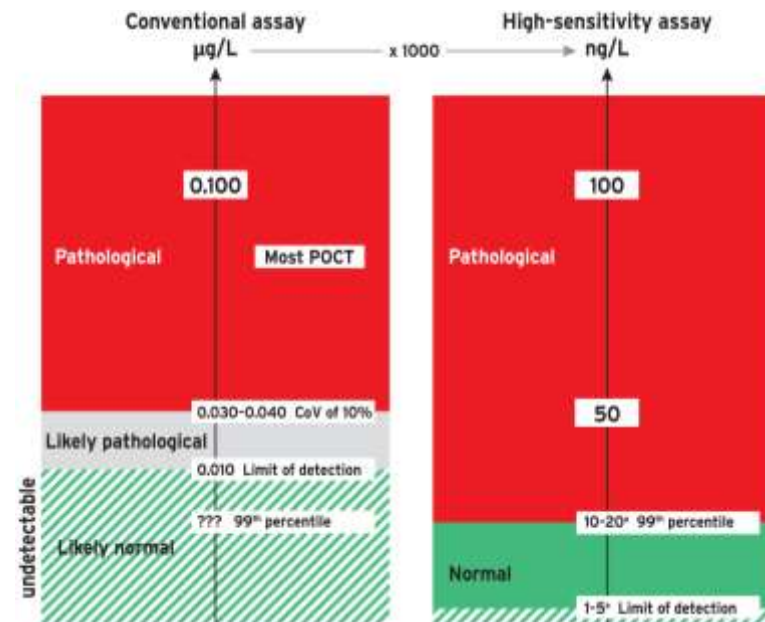


Figure 6-4: Diagnostic algorithm and triage in acute coronary syndrome. Value of high-sensitivity cardiac troponin. hs-cTn assays (right) are reported in ng/L and provide identical information as conventional assays (left, reported in mcg/L) if the concentration is substantially elevated, e.g., above 100 ng/L. In contrast, only hs cTn allows a precise differentiation between 'normal' and mildly elevated. Therefore, hs-cTn detects a relevant proportion of patients with previously undetectable cardiac troponin concentrations with the conventional assay who have hs-cTn concentrations above the 99th percentile possibly related to AMI. ??? = unknown due to the inability of the assay to measure in the normal range. **A)** The limit of detection varies among the different hs-cTn assays between 1 ng/L and 5 ng/L. Similarly, the 99th percentile varies among the different hs-cTn assays, mainly being between 10 ng/L and 20 ng/L. **Source:** 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

(1) A very small group of individuals have heterophile antibodies that agglutinate with the murine antibodies used in the troponin assay, causing the very rare "falsely positive troponin elevation". These patients have chronic troponin elevation discrepant with the stable clinical setting. An alternative troponin assay or a special heterophilic blocking reagent is used for confirmation.

- **Operationalizing criteria for myocardial injury and infarction:**

Blood samples for the measurement of cTn should be drawn on first assessment (designated as 0 h) and repeated 3–6 h later, or earlier with hs-cTn assays. The sampling interval will impact the clinical cutoff at baseline and what is determined to be a pathological rise and/or fall of the biomarker.

Sampling beyond 6 h may be required if further ischaemic episodes occur, or in high-risk patients.

Strategies employing either very low levels of hs-cTn on presentation or the lack of any change and persistently normal hs-cTn values over a 1–2 h period after presentation have been advocated to exclude acute myocardial injury, and MI as well.

A single sample rule out strategy using a very low value (in many cases the LoD of the assay) has high sensitivity for myocardial injury and therefore high negative predictive value to exclude MI.

The clinical specificity and positive predictive value of such 1–2 h sampling approaches for ruling in MI are limited by the substantial proportion of individuals who meet the proposed biomarker criteria with diagnoses other than MI. Thus, the use of a rapid rule in/out MI protocol does not absolve the clinician from considering other causes of acute myocardial injury.

Clinical presentations of myocardial infarction:

If myocardial ischaemia is present clinically or detected by ECG changes together with myocardial injury (manifested by a rising and/or falling pattern of cTn values), a diagnosis of acute MI is appropriate.

If myocardial ischaemia is not present clinically, then elevated cTn levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling, or related to more chronic ongoing injury if the pattern is unchanging.

It is usual practice to designate MI in patients with chest discomfort or other ischaemic symptoms, who develop new ST segment elevations in two contiguous leads or new bundle branch blocks with ischaemic repolarization patterns as an ST-elevation MI (STEMI). In contrast, patients without ST-segment elevation at presentation are usually designated non-ST-elevation MI (NSTEMI).

In addition to these categories, MI may be classified into various types based on pathological, clinical, and prognostic differences, along with different treatment strategies.

Myocardial infarction type 1:

MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 MI.

The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly, and the dynamic thrombotic component may lead to distal coronary embolization resulting in myocyte necrosis.

Plaque rupture may not only be complicated by intraluminal thrombosis but also by haemorrhage into the plaque through the disrupted surface.

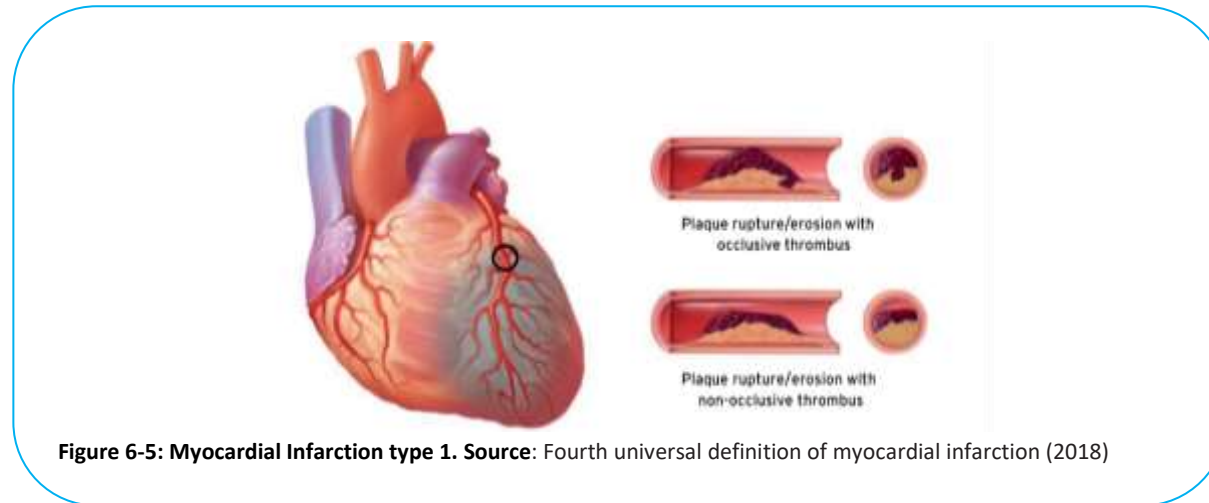
It is essential to integrate the ECG findings with the aim of classifying type 1 MI into STEMI or NSTEMI in order to establish the appropriate treatment according to current Guidelines.

Criteria for type 1 MI:

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy ⁽¹⁾.

(1) *Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis ± intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.*



Myocardial infarction type 2:

Ischemic myocardial injury in the context of a mismatch between oxygen supply and demand.

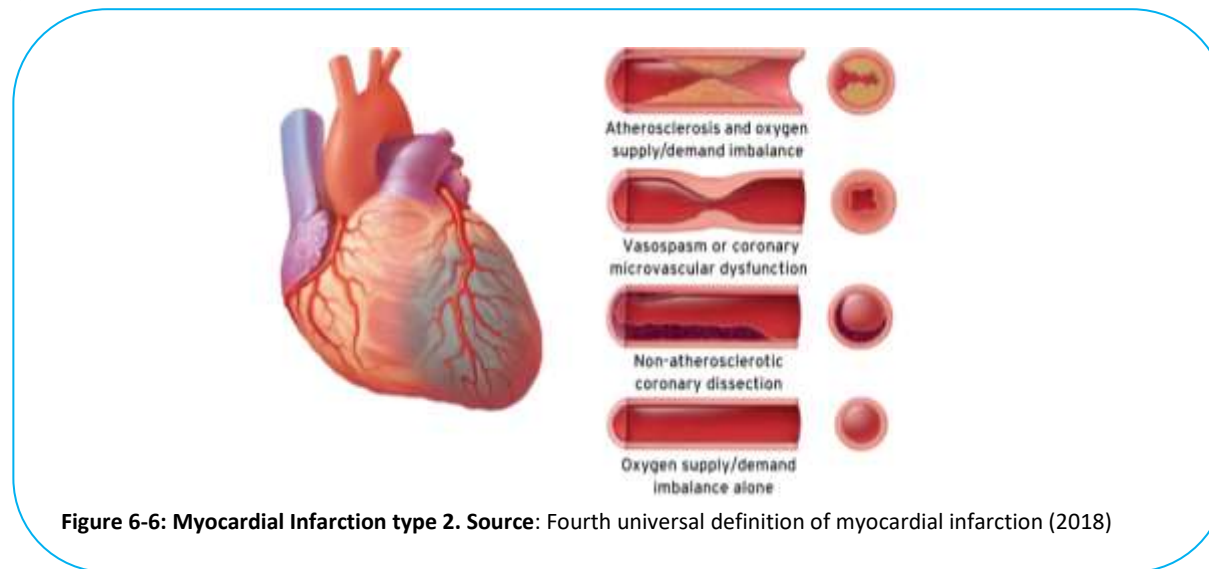
This may occur in the context of atherosclerosis ⁽¹⁾ and an oxygen supply/demand imbalance, with an oxygen supply/demand imbalance alone, secondary to vasospasm or coronary microvascular dysfunction, or secondary to non-atherosclerotic coronary dissection. These causes of Type 2 MI can be divided into those with underlying coronary (e.g. coronary embolus, dissection, spasm, microvascular dysfunction) or non-coronary mechanisms (supply demand mismatch due to hypoxia, hypotension, anaemia, tachycardia, bradycardia). Type 2 MI is common and associated with a prognosis similar to Type 1 MI ⁽²⁾.

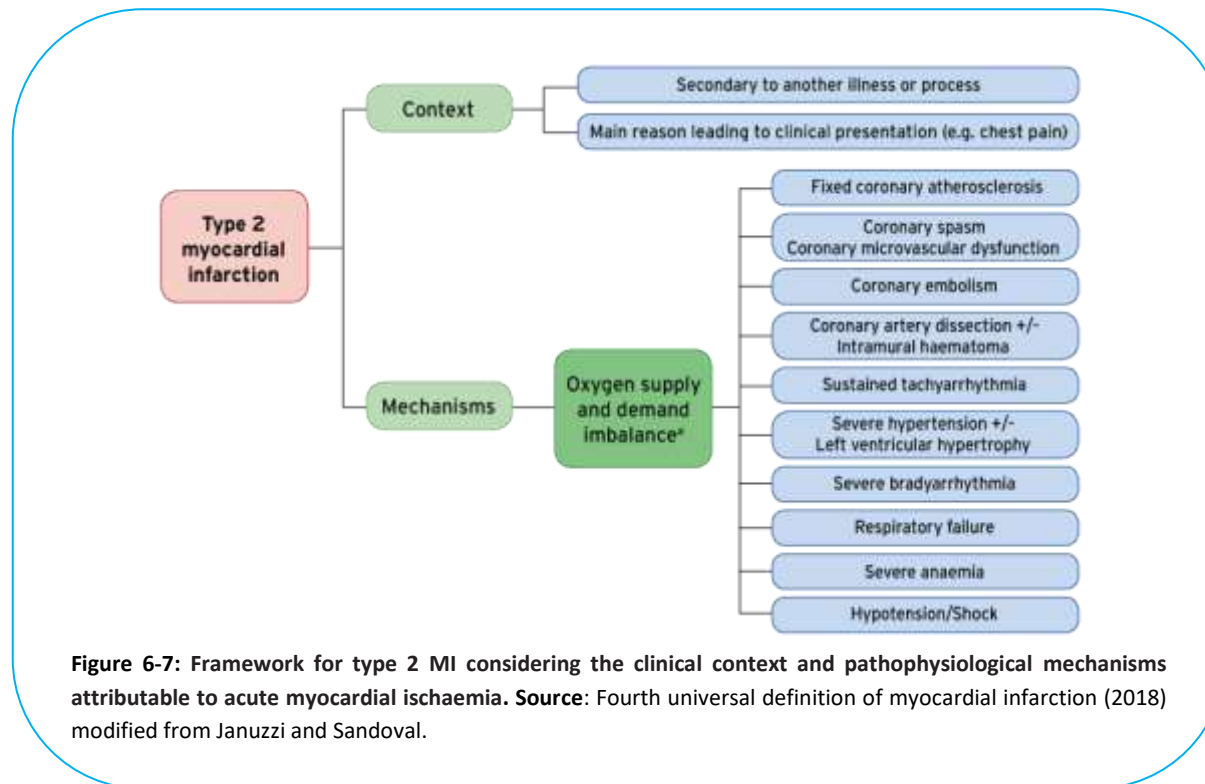
Criteria for type 2 MI:

- (1) About half of patients with type 2 MI have underlying CAD, but the coronary plaques are stable without acute rupture or thrombosis. So, antithrombotic therapy and coronary angiography are not warranted.
- (2) The prognosis was benign in patients with type 2 MI without underlying CAD: no cardiac mortality and 0.8% overall mortality at 3 months. Conversely, patients with type 2 MI and underlying CAD had a cardiac mortality comparable to type 1 MI at 3 months (~4% vs. 5%), and an overall mortality higher than type 1 MI (9 vs 6%) (due to older age, more comorbidities and higher BNP).

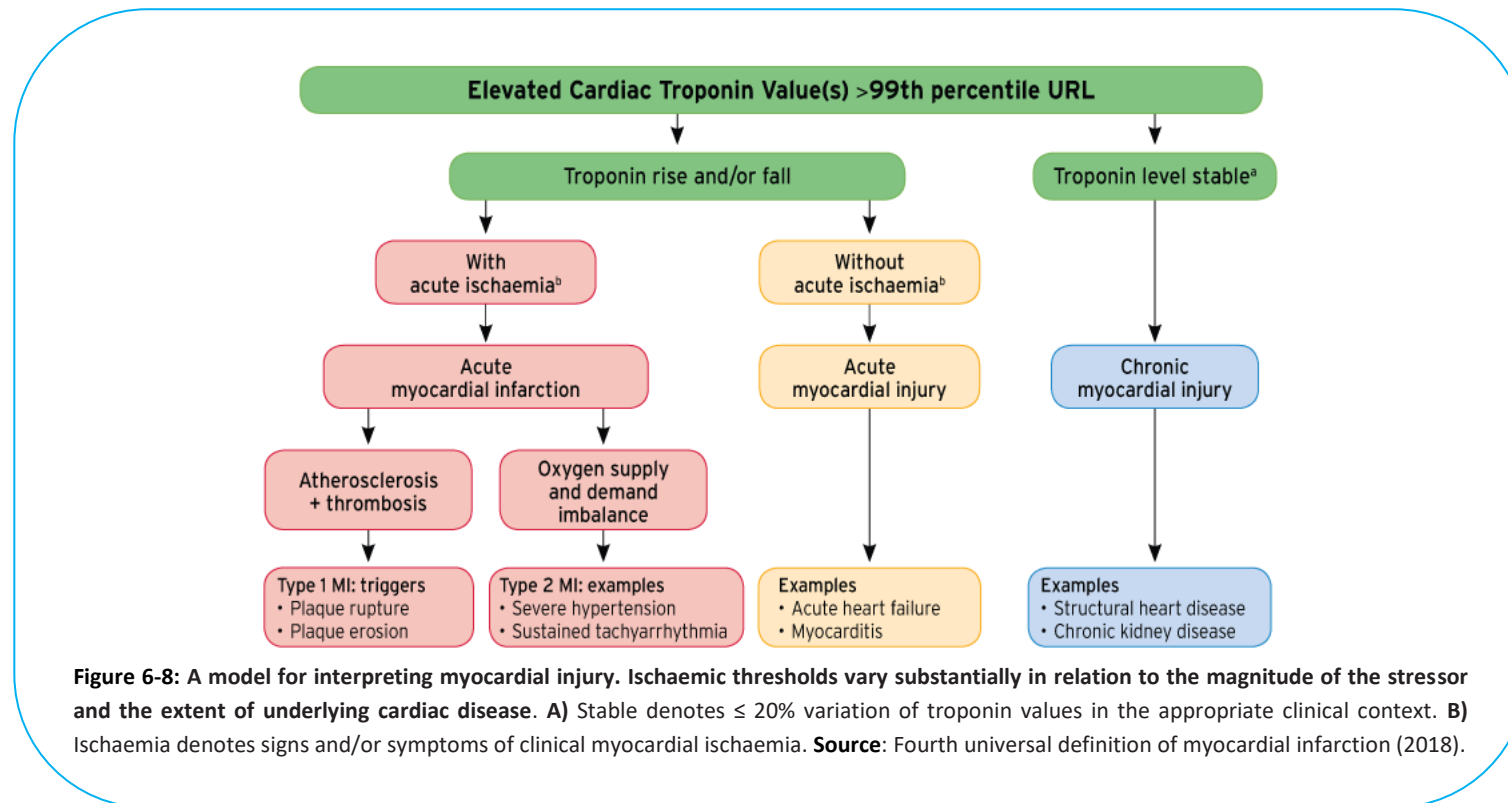
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.





Type 2 MI and myocardial injury are frequently encountered in clinical practice and both are related to a poor outcome. A conceptual model to facilitate the clinical distinction between acute ischaemic myocardial injury with or without an acute atherothrombotic event (type 1 or type 2 MI) vs. conditions without acute ischaemic myocardial injury is displayed in Figure below.



Myocardial infarction type 3:

The detection of cardiac biomarkers in the blood is fundamental for establishing the diagnosis of MI. However, patients can manifest a typical presentation of myocardial ischaemia/infarction, including presumed new ischaemic ECG changes or ventricular fibrillation, and die before it is possible to obtain blood for cardiac biomarker determination; or the patient may succumb soon after the onset of symptoms before an elevation of biomarker values has occurred. Such patients are designated as having a type 3 MI, when suspicion for an acute myocardial ischaemic event is high, even when cardiac biomarker evidence of MI is lacking.

Criteria for type 3 MI:

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Coronary procedure-related myocardial injury

Cardiac procedural myocardial injury related to coronary revascularization procedures, whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), may be temporally related to the procedure itself, reflecting periprocedural issues, or may occur later reflecting complications of a device, such as early or late stent thrombosis or in-stent restenosis for PCI, or graft occlusion or stenosis with CABG.

The occurrence of procedural myocardial injury can be detected by the measurement of cTn before the procedure and repeated 3 – 6 h later. Where the second value is rising, further sampling should be performed to document the peak cTn value. Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal ($\leq 99^{\text{th}}$ percentile URL), or if they are stable or falling.

Criteria for cardiac procedural myocardial injury:

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values ($> 99^{\text{th}}$ percentile URL) in patients with normal baseline values ($\leq 99^{\text{th}}$ percentile URL) or a rise of cTn values $> 20\%$ of the baseline value when it is above the 99^{th} percentile URL but it is stable or falling.

Myocardial Infarction type 4 (MI associated with PCI):

Standalone post-procedural increases of cTn values are sufficient to establish a diagnosis of procedural myocardial injury but not for the diagnosis of type 4a MI.

○ Myocardial Infarction type 4a (PCI-related MI ≤ 48 h after the index procedure):

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99^{th} percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (\leq

20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization ⁽¹⁾.

Other criteria that meet the definition of type 4a MI, regardless of hs-cTn or cTn values, are the development of new pathological Q waves or autopsy evidence of recent procedure related thrombus in the culprit artery.

○ **Myocardial Infarction type 4b (Stent/scaffold thrombosis associated with PCI):**

A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure.

The following temporal categories are suggested: Acute, 0–24 h; Subacute, > 24 h to 30 days; Late, > 30 days to 1 year; and Very late > 1 year after stent/scaffold implantation.

○ **Myocardial Infarction type 4c (Restenosis associated with associated with PCI):**

Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

(1) *Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.*

Myocardial Infarction type 5 (MI associated with CABG):

Numerous factors can lead to procedural myocardial injury during a CABG procedure. Many of them are related to the details of the cardiac preservation, the extent of the direct traumatic injury to the myocardium, as well as any potential ischaemic injury. For that reason, increases in cTn values should be expected after all CABG procedures.

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable ($\leq 20\%$ variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;⁽¹⁾
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

Myocardial injury and infarction associated with other cardiac procedures:

Cardiac procedures such as transcatheter valve interventions may cause myocardial injury, both by direct trauma to the myocardium and by creating regional ischaemia secondary to coronary obstruction or embolization. Ablation of arrhythmias involves controlled procedural myocardial injury by application of warming or cooling of the tissue. The extent of procedural myocardial injury can be assessed by serial cTn measurements. Increases of cTn values in this context should be considered as a procedural myocardial injury and not labelled as an MI unless the biomarker criteria and one of the ancillary criteria for acute myocardial ischaemia listed for type 5 MI are present.

Electrocardiographic detection of MI:

The ECG is an integral part of the diagnostic workup of patients with suspected MI, and should be acquired and interpreted promptly (i.e., target within 10 min) after first medical contact.

(1) Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but <10 times the 99th percentile URL.

Acute myocardial ischaemia is often associated with dynamic changes in ECG waveform and serial ECG acquisition can provide critical information, particularly if the ECG at initial presentation is non-diagnostic.

Recording several standard ECGs with fixed electrode positions at 15 – 30 min intervals for the initial 1 – 2 h, or the use of continuous computer-assisted 12-lead ECG recording (if available) to detect dynamic ECG changes, is reasonable for patients with persistent or recurrent symptoms or an initial non-diagnostic ECG.

The J-point (junction between QRS termination and ST-segment onset) is used to determine the magnitude of the ST-segment shift with the onset of the QRS serving as the reference point. In patients with a stable baseline, the TP segment (isoelectric interval) is a more accurate method to assess the magnitude of ST segment shift, and in distinguishing pericarditis (PTa depression) from acute myocardial ischaemia. Tachycardia and baseline shift are common in the acute setting and can make this determination difficult. Therefore, QRS onset is recommended as the reference point for J-point determination.

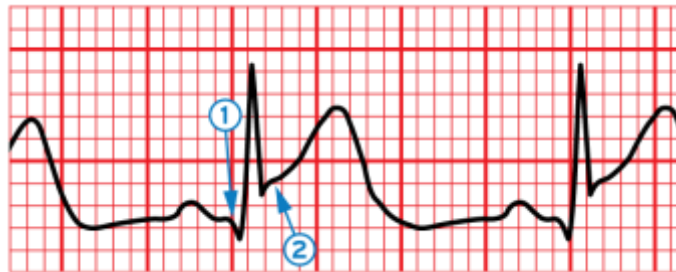


Figure 6-9: Electrocardiogram example of ST-segment elevation. The initial onset of the Q wave shown by arrow 1 serves as the reference point and arrow 2 shows the onset of the ST-segment or J-point. The difference between the two identifies the magnitude of displacement. Measurements of both arrows should be made from the top of the electrocardiogram line tracing. **Source:** Fourth universal definition of myocardial infarction (2018).

Table 6-3: ECG manifestations suggestive of acute myocardial ischaemia (in the absence of BBB and LVH)

ST-elevation:

New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥ 2 mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age.⁽¹⁾

ST-depression and T wave changes:

*New horizontal or downsloping ST-depression ≥ 0.5 mm in two contiguous leads⁽²⁾ and/or
T inversion > 1 mm in two contiguous leads with prominent R wave or R/S ratio > 1 .*

Application of supplemental electrocardiogram leads:

Supplemental leads, as well as serial ECG recordings, should be deployed with a very low threshold in patients who present with ischaemic chest pain and a non-diagnostic initial ECG.

ECG evidence of myocardial ischaemia in the distribution of a left circumflex artery is often overlooked. Isolated ST-segment depression ≥ 0.5 mm in leads V1–V3 may indicate left circumflex occlusion and can best be captured using posterior leads at the fifth intercostal space (V7 at the left posterior axillary line, V8 at the left mid-scapular line, and V9 at the left paraspinal border). A cut-off point of 0.5 mm ST-elevation is recommended in leads V7–V9; specificity is increased at a cut-off point ≥ 1 mm ST-elevation and this cut-off point should be used in men < 40 years old.

In patients with inferior and suspected right ventricular infarction, leads aVR or V1 may exhibit ST-segment elevation ≥ 1 mm. The early recording of right precordial leads V3R and V4R should be performed, since ST-elevation ≥ 0.5 mm (≥ 1 mm in men < 30 years old) provides supportive criteria for the diagnosis.

Changes in right precordial leads may be transient, and an absence of ECG changes in leads V3R and V4R does not exclude right ventricular infarction.

(1) When the magnitudes of J-point elevation in leads V2 and V3 are registered from a prior electrocardiogram, new J-point elevation ≥ 1 mm (as compared with the earlier electrocardiogram) should be considered an ischaemic response.

(2) ST depression is common during fast tachyarrhythmias and after their conversion to sinus rhythm (cardiac memory), even in the absence of ischemia. It is not specific for MI definition in this setting.

Imaging techniques:

Imaging techniques can be useful in the diagnosis of acute MI because of the ability to detect wall motion abnormalities or loss of viable myocardium in the presence of elevated cardiac biomarker values.

Demonstration of new loss of myocardial viability in the absence of non-ischaemic causes supports the diagnosis of MI. Normal function practically excludes significant MI, but a small MI cannot be ruled out. Thus, imaging techniques are useful for early triage and discharge of patients with suspected MI. However, if biomarkers have been measured at appropriate times and are normal, this excludes acute MI and takes precedence over the imaging criteria.

Echocardiography:

The strength of echocardiography is the combined assessment of cardiac structure and function, in particular myocardial thickness, thickening/thinning, and motion. Regional wall motion abnormalities induced by ischaemia can be detected by echocardiography almost immediately after onset when > 20% transmural myocardial thickness is affected. These abnormalities, when new and without alternative aetiology, support the diagnosis of MI when cTn values show a rising and/or falling pattern. Echocardiography also allows detection of non-coronary cardiac pathologies known to cause chest pain, e.g. acute pericarditis, severe aortic stenosis, and hypertrophic cardiomyopathy among others.

The technique is useful in diagnosing mechanical complications in patients with MI and haemodynamic compromise (shock), or other potentially fatal entities such as acute aortic dissection or massive pulmonary embolism where the clinical presentation might be similar to that seen with acute MI.

Cardiac MRI (CMR):

Although less commonly used in the acute setting, CMR has similar capabilities to echocardiography in suspected MI with higher tissue contrast and resolution.

Paramagnetic contrast agents can be used to assess myocardial perfusion and the increase in extracellular space that is associated with the fibrosis of prior MI (detected by LGE). These techniques have been used in the setting of acute MI and localized delay in contrast enhancement is able to detect even small areas of subendocardial MI, thought to be as little as 1 g.

CMR also has the ability to identify the presence and extent of myocardial oedema/inflammation, allowing the distinction of acute vs. chronic myocardial injury.

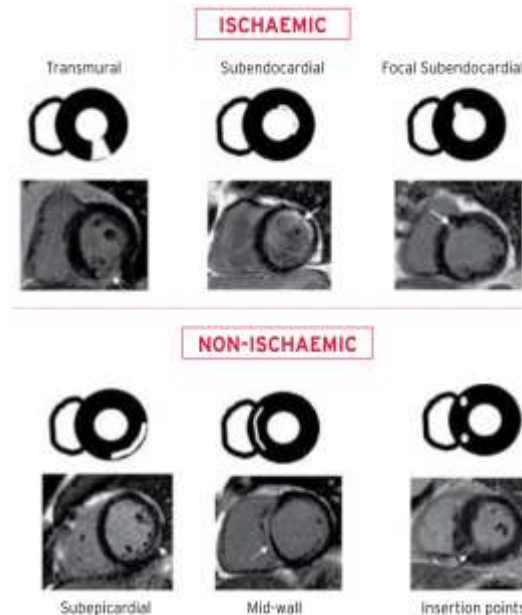


Figure 6-10: Post-contrast cardiac magnetic resonance images. The gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scarring (white arrows). The different patterns of scarring are divided into ischaemic and non-ischaemic. Typically, an ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely, a non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel). **Source:** Fourth universal definition of myocardial infarction (2018).

Prior or silent/unrecognized MI

Asymptomatic patients who develop new Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging that cannot be directly attributed to an interim coronary revascularization procedure or an ACS admission, should be termed 'silent or unrecognized MI'.

Criteria for prior or silent/unrecognized MI: Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Pathological Q waves, with or without symptoms, in the absence of non-ischaemic causes;
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology;
- Pathological findings of a prior MI.

ECG changes associated with prior MI (In the absence of LVH and LBBB):

- Q wave criteria associated with MI and increased relative risk of death are:
 - Any Q wave in leads V2–V3 > 0.02 s or QS complex in leads V2–V3.
 - Q wave ≥ 0.03 s and ≥ 1 mm deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF) ⁽¹⁾.
- R wave > 0.04 s in V1–V2 and R/S > 1 with a concordant positive T wave in absence of conduction defect.

The specificity of the ECG diagnosis for MI is greatest when: **(i)** Q waves occur in several leads; or **(ii)** lead groupings; or **(iii)** are > 0.04 s; or **(iv)** when the Q waves are associated with ST deviations or T wave changes in the same leads.

Re-infarction vs. Recurrent MI

- Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, the second event is **re-infarction**. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a **recurrent MI**.
- The ECG diagnosis of suspected re-infarction following the initial MI may be confounded by the initial evolutionary ECG changes. Re-infarction should be considered when ST-elevation ≥ 1 mm recurs or new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischaemic symptoms.
- In patients where re-infarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn is recommended. A second sample should be obtained 3–6 h later or earlier with more sensitive cTn assays.

(1) The same criteria are used for supplemental leads V7–V9.

If the cTn concentration is elevated, but stable or decreasing at the time of suspected re-infarction, the diagnosis of re-infarction requires a > 20% increase of the cTn value in the second sample.

If the initial cTn concentration is normal, the criteria for new acute MI apply.

Myocardial injury and infarction in concomitant diseases

Myocardial injury and infarction associated with non-cardiac procedures:

- Perioperative MI is one of the most important complications in major non-cardiac surgery and it is associated with a poor prognosis.
- Most patients who have a perioperative MI will not experience ischaemic symptoms due to anaesthesia, sedation, or pain-relieving medications.
- Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the aetiology of elevated postoperative values, a baseline pre-operative value is necessary to determine whether the increase is acute or more chronic. However, a diagnosis of MI still requires, in addition to an increase of cTn values, evidence of myocardial ischaemia that may be evident from the periand post-operative period, e.g. ST-segment changes on telemetry/ECG, repeated episodes of hypoxia, hypotension, tachycardia, or imaging evidence of MI. In the absence of evidence for acute myocardial ischaemia, a diagnosis of acute myocardial injury is more appropriate.

Myocardial injury or infarction associated with HF:

- Depending on the assay used, detectable to clearly elevated cTn values being indicative of myocardial injury may be seen in patients with HF, both with reduced EF and with preserved EF.
- Acute HF often leads to troponin elevation because of microcirculatory compression by the high LVEDP and because of direct cardiomyocyte injury from wall stretch and neurohormones. An elevated troponin, by itself, does not establish the diagnosis of ACS in a patient presenting with HF. In fact, most troponin elevations in HF are not even type 2 MI, but rather “non- MI troponin elevation”. Yet, if CAD has not been addressed previously, coronary angiography is still warranted to address the underlying etiology of HF, after diuresis and preferably before discharge, with early revascularization if appropriate.

- Conversely, acute HF with ischemic ST changes, new Q waves, severe troponin rise, or new segmental akinesis may be considered type 1 MI and treated as such, unless CAD has been ruled out recently. About 30% of acute HF presentations are triggered by ischemia.

Myocardial injury and/or infarction associated with kidney disease:

- Many patients with chronic kidney disease (CKD) have elevation of cTn values. This is not related to reduced renal clearance of troponin, a marginal effect at best. It is rather due to increased ventricular pressure, small-vessel coronary obstruction, anaemia, hypotension, and possibly direct toxic effects on the myocardium associated with the uraemic state.
- Studies suggest that serial changes in cTn levels are equally effective in diagnosing MI in patients with CKD and in those with normal renal function. However, if a rising and/or falling pattern is present then the aetiology of the abnormal cTn values could be acute volume overload, congestive HF, or MI. If a rising and falling pattern is seen, and it is accompanied by ischaemic symptoms, new ischaemic ECG changes, or loss of viable myocardium on imaging, a diagnosis of acute MI is likely.

Spontaneous Coronary Artery Dissection (SCAD)

SCAD is an infrequent cause of ACS in general, but accounts for a significant proportion of ACS cases in young/middle-aged women.

- **Definition:** SCAD is defined as a non-atherosclerotic, non-traumatic separation of the coronary arterial tunics secondary to bleeding inside the media (vasa vasorum haemorrhage) or intimal tear, which creates a false lumen, coronary compression, and downstream myocardial ischaemia.
- **Precipitating Factors:** intense exercise (especially isometric), intense emotional stress, valsalva and hormonal fluctuations.
- **Associated conditions:** Pregnancy, migraine, connective tissue disorders, inherited aortopathies, peripheral fibromuscular dysplasia (renal ~70%, iliac ~50%, carotid ~50%), and intracranial aneurysms (~15-20%). Therefore, screening with abdominal CT and carotid-cerebral CT angiography is warranted.
- **Features:** SCAD has the following features:
 - Occurs in women (95%), mainly young and middle-aged women, it may rarely be seen in men.

- SCAD is the cause of up to 4% of patients with ACS. SCAD presents as NSTEMI (~ 60%) or STEMI (~ 40%).
- Typically involves the mid- to distal coronary segments, most commonly the LAD, and may involve multiple coronary arteries (~10-20%). Proximal or left main involvement is rare (~8%).
- Is highly associated with coronary tortuosity (78%). The same collagen fragility that predisposes to wall disruption also facilitates coronary elongation.
- **Classification:** Diagnosis of SCAD is made at the time of coronary angiography. It can be graded into:
 - **Type 1:** The classic description is of a longitudinal filling defect, representing the radiolucent intimal flap. There is often contrast staining of the arterial wall with appearance of a double lumen.
 - **Type 2** (most common, 67% of cases): Diffuse long smooth tubular lesions (due to intramural haematoma) with no visible dissection plane that can result in complete vessel occlusion. Lesions are typically > 30 mm in length with an abrupt change in vessel diameter between normal and diseased segments. There is no response to intracoronary nitrates and there are no atherosclerotic lesions in other coronary segments.
 - **Type 3:** Multiple focal tubular lesions due to intramural haematoma that mimic atherosclerosis. Intravascular imaging is required to make the diagnosis.
- **Treatment:**
 - In patients without active ischemia, without total occlusion, and with TIMI 2 or 3 flow: conservative management as 70-97% of SCAD spontaneously heal on follow-up angiography ≥ 35 days. Conservative treatment consists of:
 - Inpatient monitoring for 3-5 days.
 - Beta-blockers reduce recurrence.
 - DAPT for at least 2 to 4 weeks after SCAD and then continue low-dose aspirin alone for a total of 3 to 12 months, encompassing the timeframe for SCAD healing. In individuals at higher risk of bleeding events, consideration of aspirin alone or no antiplatelet therapy is not unreasonable.
 - Discontinue systemic anticoagulation and glycoprotein IIb-IIIa inhibitors once SCAD is diagnosed unless there is apparent intraluminal thrombus or other indications for systemic anticoagulation.

- There is no evidence that hyperlipidemia is relevant to the pathophysiology of SCAD recurrence risk. Lipid-lowering therapy is therefore usually reserved for patients who have hyperlipidemia or whose risk profile would warrant treatment according to primary prevention guidelines.
- In patients with ongoing STEMI, total occlusion, or hemodynamic compromise:
 - PCI is recommended ⁽¹⁾. Low- pressure balloon dilatation may be tried as a stand-alone strategy to re-establish flow, avoiding long stenting in a pathology that will heal on its own.
 - CABG is recommended when dissection affects the left main or two proximal vessels, if PCI is not feasible or unsuccessful, and if there are symptoms and signs of ongoing myocardial ischaemia. CABG is hampered by distal vessel involvement and by a high rate of graft closure (70%) on long-term follow up, as native disease regresses. For this reason, vein grafts should be considered in these patients in order to preserve arterial conduits for future use.
- **Progression and follow-up:**
 - SCAD almost always heals, yet acute extension may be seen in ~5-10% of cases *in the first week*, before eventual healing; thus, ECG signs of ongoing or recurrent ischemia ⁽²⁾ may justify repeat coronary angiography or CT.
 - In-hospital and long-term survival is very favourable in non-pregnancy SCAD (< 2% in-hospital mortality).
 - There is a 10-30% risk of recurrence at 1-3 years, and 30% at 5 years. Recurrence is reduced with: β - blockers (2/3 reduction), avoidance of emotional and physical triggers, and hormonal therapy.
 - Peripartum SCAD is more severe clinically than non-pregnancy SCAD. SCAD, even non-pregnancy SCAD, generally contraindicates future pregnancies.

Table 6-4: ESC Recommendations for management of spontaneous coronary artery dissection:

Recommendations

Class Level

(1) *The outcomes of PCI in SCAD are less predictable with higher rates of complications and suboptimal outcomes, including an elevated risk of iatrogenic dissection and abrupt vessel occlusion. Hematoma propagation occurs in up to one-third of PCI cases, frequently requiring the use of multiple unplanned stents.*

(2) *Note that persistent pain, by itself, does not necessarily imply ischemia, as the dissection process may be painful by itself.*

In patients with SCAD, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.

I

C

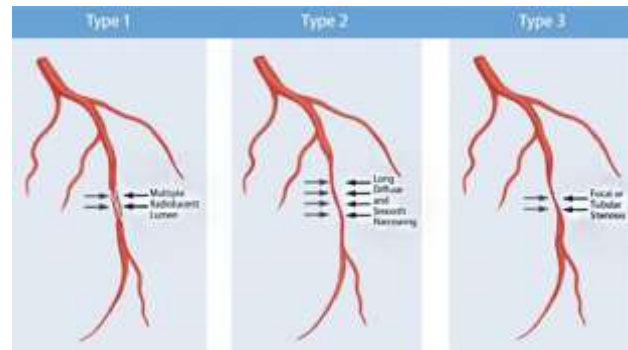


Figure 6-11: SCAD Classification. Source: Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, Mancini GJ. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. Journal of the American College of Cardiology. 2017 Aug 29;70(9):1148-58.

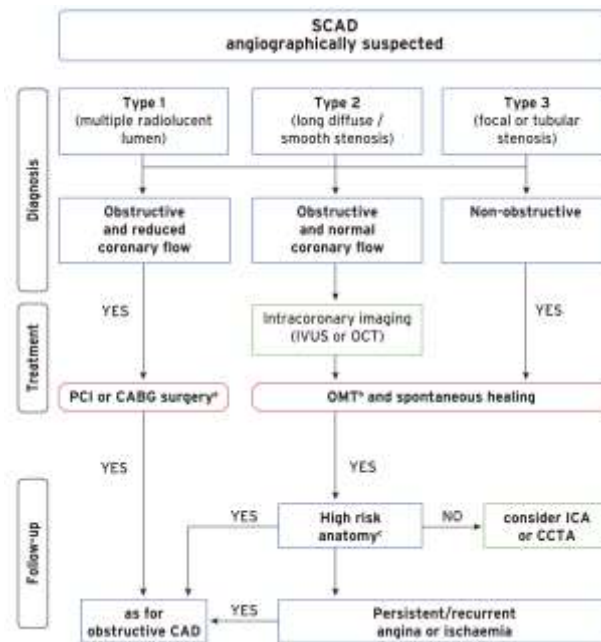


Figure 6-12: Diagnosis and treatment of patients with NSTEMI-ACS related to spontaneous coronary artery dissection. A) Selection of revascularization strategy for high-risk anatomy according to local expertise. B) Beta-blocker recommended while benefit of DAPT is questionable. C) Left main or proximal LAD or LCx or RCA, multivessel SCAD. Source: 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

Myocardial infarction with non-obstructive coronary arteries (MINOCA)

MINOCA refers to the clinical situation when a patient presents with symptoms suggestive of ACS, demonstrates troponin elevation, and has non-obstructive coronary arteries at the time of coronary angiography (defined as coronary artery stenosis < 50% in any major epicardial vessel).

The reported prevalence of MINOCA varies widely across studies (from around 1% to 14% of patients with ACS undergoing angiography). It is more common in women, as well as in patients presenting with NSTEMI compared with those presenting with STEMI.

MINOCA can be considered as an umbrella term that encompasses a heterogeneous group of underlying causes. This includes both coronary and non-coronary pathologies, with the latter including both cardiac and extra-cardiac disorders.

Criteria for diagnosis:

The diagnosis of MINOCA is made immediately upon coronary angiography in patient presenting with features consistent with an AMI, as detailed by the following criteria:

1. Universal AMI criteria ⁽¹⁾.
2. Non-obstructive coronary arteries on angiography, defined as no coronary artery stenosis \geq 50% in any potential IRA ⁽²⁾.
3. No clinically overt specific cause for the acute presentation.

Causes:

When a diagnosis is not established following coronary angiography, MINOCA represents a working diagnosis as opposed to a final diagnosis. It is vital for clinicians to perform further assessments and investigations to establish the underlying cause of the MINOCA, which will allow a final diagnosis to be established and patients to be managed appropriately. Failure to identify the underlying cause of MINOCA may result in inadequate or inappropriate therapy.

(1) Beware of the misuse of the term MINOCA. The term MINOCA does not apply to patients with type 2 MI context or non-MI troponin elevation. It only applies to those with type 1 MI presentation.

(2) 50% is considered obstructive in MI, unlike the 70% cutoff in stable CAD.

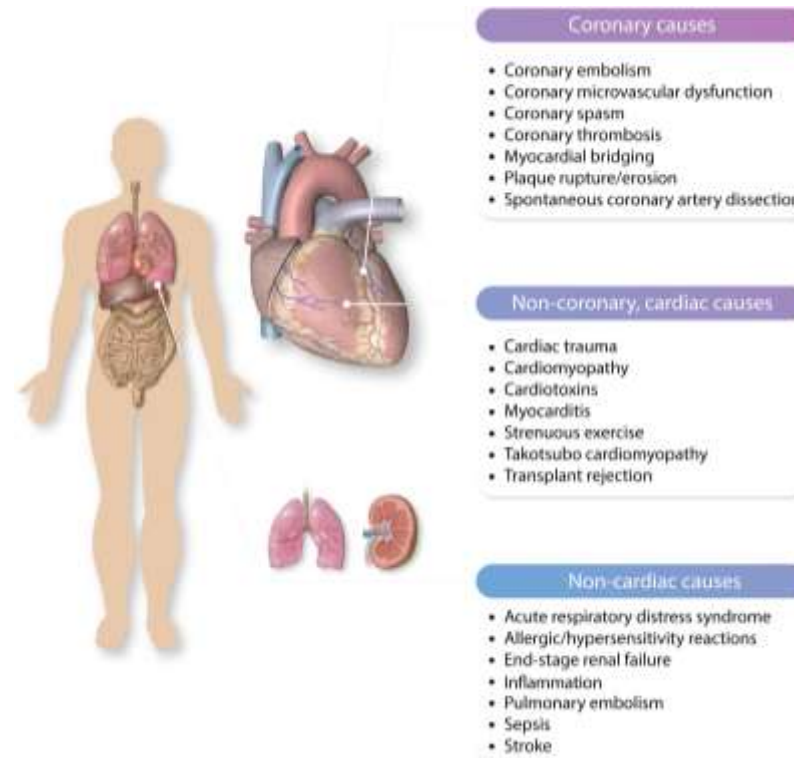


Figure 6-13: Underlying causes for patients with a working diagnosis of myocardial infarction with non-obstructive coronary arteries. This figure outlines some of the potential differential diagnoses in patients with a working diagnosis of MINOCA after coronary angiography, but this list is not exhaustive. **Source:** 2023 ESC Guidelines for the management of acute coronary syndromes.

Work-up:

- ICA is the recommended definitive diagnostic test for ACS patients.

- If the underlying cause of MINOCA is not established using ICA alone, further evaluation using left ventriculography (including measurement of LV end-diastolic pressure), functional assessment with measurement of microvascular function/coronary reactivity, and intravascular imaging can be useful to identify the underlying cause.
- If the underlying cause of MINOCA is not established using functional coronary angiography, then non-invasive imaging (i.e. echocardiography, CMR, CT) is recommended, as clinically appropriate.

CMR is one of the key diagnostic tools to determine the underlying cause of MINOCA. CMR can identify the underlying cause in up to 87% of patients with a working diagnosis of MINOCA and should be performed as soon as possible after presentation in these patients to maximize its diagnostic yield, ideally during the index admission.

| Table 6-5: ESC Recommendations for MINOCA: | | |
|---|---------------------|---------------------|
| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
| <i>In patients with a working diagnosis of MINOCA, CMR imaging is recommended after invasive angiography if the final diagnosis is not clear.</i> | I | B |
| <i>Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines.</i> | I | B |
| <i>In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.</i> | I | C |

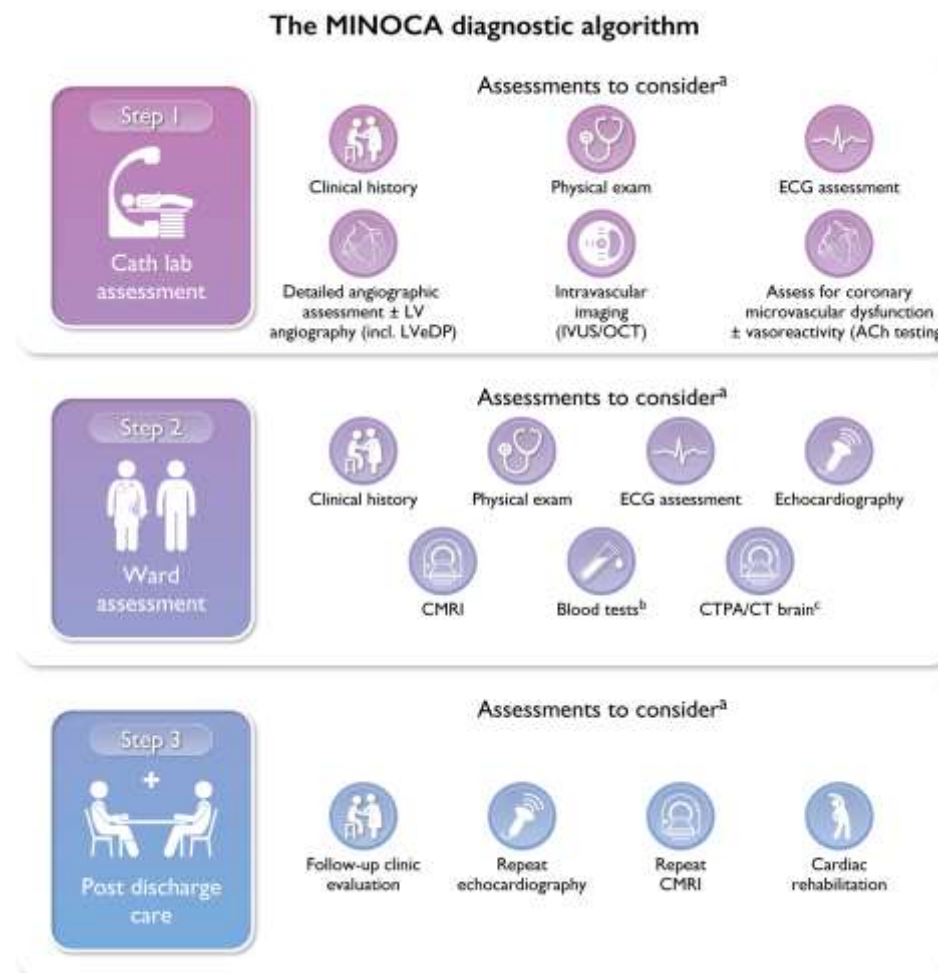


Figure 6-14: Evaluation of patients with a working diagnosis of MINOCA.

Patients presenting with STEMI present directly to catheter lab (1). In this context, when non-obstructive coronary arteries are identified then further assessment should be considered. When patients are subsequently admitted to the ward then investigations as shown in (2) should be considered.

Patients presenting with NSTEMI-ACS or UA are often stabilized on the ward (2) prior to transfer to the cath lab (1). In this context the order in which the investigations are carried out will vary depending on the location these patients are managed during first contact.

MINOCA patients require follow-up review (3) and may require repeat assessment using echocardiography and magnetic resonance imaging, depending on the initial findings.

A) Options for adjunctive tests. Patients will not require all investigations but instead the appropriate tests should be selected based on their presentation and clinical course. **B)** Examples of potential blood tests

Refrences and suggested readings:

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Chapter 7:

ST-Elevation Myocardial Infarction

Epidemiology:

Worldwide, coronary artery disease (CAD) is the single most frequent cause of death. Over seven million people every year die from CAD, accounting for 12.8% of all deaths. The incidence of STEMI appears to be declining, while there is a concomitant increase in the incidence of non-STEMI.

There is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women.

The mortality of STEMI is influenced by many factors, among them: age, Killip class, time delay to treatment, mode of treatment, history of prior MI, DM, renal failure, number of diseased coronary arteries, and ejection fraction.

Several recent studies have highlighted a fall in acute and long-term mortality following STEMI, in parallel with greater use of reperfusion therapy, primary PCI, modern antithrombotic therapy and secondary prevention treatments.

Emergency care:

Management of AMI starts at the point of **first medical contact (FMC)**, defined as the point at which the patient is either initially assessed by a paramedic or physician or other medical personnel in the pre-hospital setting, or the patient arrives at the hospital emergency department.

- This is usually based on a **history of chest pain** lasting for ≥ 20 min, not responding to nitroglycerine radiating to the neck, lower jaw or left arm. Some patients present with less-typical symptoms, such as nausea/vomiting, shortness of breath, fatigue, palpitations or syncope. These patients tend to present later, are more likely to be women, diabetic or elderly patients.

- **ECG monitoring** should be initiated as soon as possible in all patients with suspected STEMI to detect life-threatening arrhythmias and allow prompt defibrillation if indicated.
 - A **12-lead ECG** should be obtained as soon as possible at the point of FMC:
 - **Typically**, ST-elevation measured at the J point, should be found in two contiguous leads and be:
 - ≥ 0.25 mV in men < 40 years, ≥ 0.2 mV in men > 40 years, or ≥ 0.15 mV in women in leads V_2 - V_3 .
 - ≥ 0.1 mV in other leads (in the absence of LVH or LBBB).
 - **Atypical ECG presentations** that deserve prompt management in patients with signs and symptoms of ongoing myocardial ischaemia:
 - **Bundle Branch Block:** in the presence of LBBB, the ECG diagnosis of AMI is difficult, but possible if marked ST abnormalities are present:
 - ✓ The presence of concordant ST elevation ≥ 1 mm (i.e. in leads with positive QRS deflections).
 - ✓ concordant ST depression ≥ 1 mm in V_2 - V_3 .
 - ✓ Discordant ST elevation ≥ 5 mm in leads with negative QRS.
- Importantly, in patients with clinical suspicion of ongoing myocardial ischaemia with new or presumed new LBBB, reperfusion therapy should be considered promptly, preferably using emergency coronary angiography or, if unavailable, intravenous (i.v.) thrombolysis.
- Patients with myocardial infarction and RBBB also have a poor prognosis, although RBBB usually will not hamper interpretation of ST-segment elevation.
- **Ventricular pacing:** during RV pacing, the ECG also shows LBBB, and the above rules also apply for the diagnosis of MI during pacing, but they are less specific.
 - **Isolated posterior MI:**

Acute myocardial infarction of the infero-basal portion of the heart, often corresponding to the left circumflex territory in which isolated ST-depression ≥ 0.05 mV in leads V_1 through V_3 represents the dominant finding, should be treated as a STEMI.

The use of additional posterior chest wall leads [$V_7-V_9 \geq 0.05$ mV (≥ 0.1 mV in men < 40 years old)] is recommended to detect ST elevation.

○ **Left main coronary obstruction or multivessel disease:**

ST depression ≥ 1 mm in ≥ 6 surface leads (inferolateral ST depression), coupled with ST-elevation in aVR and/or V1, suggests multivessel ischaemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.

- Blood sampling for **serum markers** is routinely carried out in the acute phase but one should not wait for the results before initiating reperfusion treatment. Troponin (T or I) is the biomarker of choice, given its high sensitivity and specificity for myocardial necrosis.

In patients who have both a clinically low or intermediate likelihood of ongoing myocardial ischaemia and a long prior duration of symptoms, a negative troponin test may help to avoid unnecessary emergency angiography in some patients.

N.B:

- In patients with inferior myocardial infarction, it is advisable to record right precordial leads (V3R and V4R) seeking ST elevation, in order to identify concomitant right ventricular infarction.
- In any case, ongoing suspicion of myocardial ischaemia -despite medical therapy- is an indication for emergency coronary angiography with a view to revascularization, even in patients without diagnostic ST-segment elevation.
- In hospitals or settings in which coronary angiography is not immediately available -provided it does not delay transfer- rapid confirmation of segmental wall-motion abnormalities by two dimensional echocardiography may assist in making a decision for emergency transfer to a PCI centre, since regional wall-motion abnormalities occur within minutes following coronary occlusion, well before necrosis. The absence of wall-motion abnormalities excludes major MI.

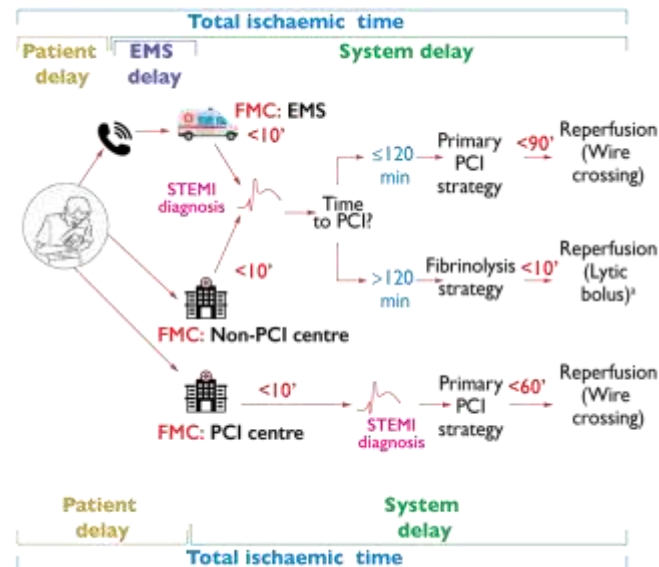


Figure 7-1: Modes of patient presentation, components of ischemia time and flowchart for reperfusion strategy selection. When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or in a non-PCI centre, the decision for choosing reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when EMS arrives to the scene. ‘ denotes minutes. **A)** Patients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus. **Source:** 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with STEMI.

Table 7-1: ESC Recommendations for Emergency management of STEMI:

| Recommendations | Class | Level |
|---|-------|-------|
| ECG monitoring: | | |
| 12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min. | I | B |

| | | |
|---|------------|----------|
| <i>ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.</i> | I | B |
| <i>The use of additional posterior chest wall leads (V₇-V₉) in patients with high suspicion of posterior MI (circumflex occlusion) should be considered.</i> | IIa | B |
| <i>The use of additional right precordial leads (V_{3R} and V_{4R}) in patients with inferior MI should be considered to identify concomitant RV infarction.</i> | IIa | B |
| Blood sampling: | | |
| <i>Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.</i> | I | C |
| Hypoxia: | | |
| <i>Oxygen is indicated in patients with hypoxaemia (SaO₂ < 90% or PaO₂ < 60 mmHg).</i> | I | C |
| <i>Routine oxygen is not recommended in patients with SaO₂ > 90%.</i> | III | B |
| Pain and Anxiety control: | | |
| <i>Titrated i.v. opioids should be considered to relieve pain. ⁽¹⁾</i> | IIa | C |
| <i>A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.</i> | IIa | C |
| Intravenous beta-blockers: | | |
| <i>Intravenous beta-blockers (preferably metoprolol) should be considered at the time of presentation in patients undergoing PPCI with no signs of acute heart failure, an SBP > 120 mmHg, and no other contraindications.</i> | IIa | A |

(1) *Titrated i.v. opioids (e.g. morphine) are the analgesics most commonly used in this context. Intramuscular injections should be avoided. Repeated doses may be necessary. Side effects include nausea and vomiting, hypotension with bradycardia, respiratory depression and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagrelor, and prasugrel), which may lead to early treatment failure in susceptible individuals. Anti-emetics may be administered concurrently with opioids to minimize nausea. The hypotension and bradycardia will usually respond to atropine and the respiratory depression to naloxone (0.1-0.2 mg i.v. every 15 min when indicated), which should always be available.*

| Cardiac arrest: | | |
|---|------------|----------|
| <i>A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI (or equivalents)</i> | I | B |
| <i>Temperature control (i.e., continuous monitoring of core temperature and active prevention of fever [i.e., > 37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation.</i> | I | B |
| <i>It is indicated that healthcare systems implement strategies to facilitate transfer of all patients in whom a MI is suspected directly to the hospital offering 24/7 PCI-mediated reperfusion therapy via one specialized EMS.</i> | I | C |
| <i>Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest.</i> | I | C |
| <i>Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended.</i> | III | B |

Reperfusion therapy:

- Patients with a working diagnosis of STEMI who present to a non-PCI centre should be immediately transferred to a PCI-capable centre for a timely PPCI strategy.
- If PPCI is not feasible within 120 min, patients should undergo immediate fibrinolysis followed by transfer to a PCI centre without waiting for signs of reperfusion.
- Pre-hospital fibrinolysis, compared with inhospital fibrinolysis, reduced early mortality by 17%, particularly when administered in the first 2 h after symptom onset.

- For patients who undergo fibrinolysis, rescue PCI is indicated if fibrinolysis fails (i.e., ST-segment resolution < 50% within 60-90 min of fibrinolytic administration) or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain. In this setting, re-administration of fibrinolysis is not beneficial and is discouraged.
- Patients with successful fibrinolysis should undergo early invasive angiography (i.e., within 2–24 h from the time of the lytic bolus injection).
- For patients presenting after 12 h from symptom onset, PPCI is preferred over fibrinolysis in all cases.

Table 7-2: Definitions of terms related to reperfusion therapy:

| Term | Definition |
|--|---|
| First Medical Contact | <i>The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (e.g., defibrillation). FMC can be either in the prehospital setting or upon patient arrival at the hospital.</i> |
| STEMI diagnosis | <i>The time at which the ECG of a patient with ischemic symptoms is interpreted as presenting ST-segment elevation or equivalent.</i> |
| Primary PCI | <i>Emergent PCI with balloon, stent or other approved device, performed on the IRA without previous fibrinolytic treatment.</i> |
| Primary PCI strategy | <i>Emergent coronary angiography and PCI of the IRA if indicated.</i> |
| Rescue PCI | <i>Emergent PCI performed as soon as possible if fibrinolysis fails (i.e., ST-segment resolution < 50% within 60-90 min of fibrinolytic administration) or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain.</i> |
| Routine early PCI strategy after fibrinolysis | <i>Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis.</i> |

| | |
|----------------------------------|---|
| Pharmacoinvasive strategy | <i>Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis).</i> |
|----------------------------------|---|

Table 7-3: Summary of important time targets:

| Intervals | Time targets |
|---|---------------------|
| <i>Maximum time from FMC to ECG and diagnosis</i> | ≤ 10 min. |
| <i>Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis)</i> | ≤ 120 min. |
| <i>Maximum time from STEMI diagnosis to wire crossing in patients presenting at primary PCI hospitals.</i> | ≤ 60 min. |
| <i>Maximum time from STEMI diagnosis to wire crossing in transferred patients.</i> | ≤ 90 min. |
| <i>Maximum time from STEMI diagnosis to bolus or infusion start of fibrinolysis in patients unable to meet primary PCI target times.</i> | ≤ 10 min. |
| <i>Time delay from start of fibrinolysis to evaluation of its efficacy (success or failure)</i> | 60-90 min. |
| <i>Time delay from start of fibrinolysis to angiography (if fibrinolysis is successful)</i> | 2-24 hours |

Table 7-4: ESC Recommendations for reperfusion therapy:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Reperfusion therapy for patients with STEMI: | | |

| | | |
|--|------------|----------|
| <i>Reperfusion therapy is recommended in all patients with a working diagnosis of STEMI (persistent ST-segment elevation or equivalents ⁽¹⁾) and symptoms of ischaemia of ≤ 12 h duration.</i> | I | A |
| <i>A PPCI strategy is recommended over fibrinolysis if the anticipated time from diagnosis to PCI is < 120 min.</i> | I | A |
| <i>If timely primary PCI (< 120 min) cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.</i> | I | A |
| <i>Rescue PCI is recommended for failed fibrinolysis (i.e., ST-segment resolution < 50% within 60-90 min of fibrinolytic administration) or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain.</i> | I | A |
| <i>Early angiography (within 24 h) is recommended if symptoms are completely relieved and ST-segment elevation is completely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-elevation).</i> | I | C |
| <i>In patients with time from symptom onset > 12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.</i> | I | C |
| <i>A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset.</i> | Ila | B |

(1) ST-elevation equivalents include: (i) Posterior STEMI (ST-segment elevation in V7–V9 or ST-segment depression in leads V1–V3, especially when the terminal T-wave is positive (ST-segment elevation equivalent), (ii) RV MI (ST-segment elevation in V3R and V4R), (iii) Multivessel or left main obstruction (ST depression ≥ 1 mm in ≥ 6 surface leads, coupled with ST-segment elevation in aVR and/or V1), (iv) Patients with BBB and a high clinical suspicion of ongoing myocardial ischaemia should be managed in a similar way to STEMI patients.

| | | |
|---|------------|----------|
| <i>In asymptomatic patients, routine PCI of an occluded IRA > 48 h after onset of STEMI is not recommended.</i> | III | A |
| Transfer/interventions after fibrinolysis: | | |
| <i>Transfer to a PCI-capable centre is recommended in all patients immediately after fibrinolysis.</i> | I | A |
| <i>Emergency angiography and PCI of the IRA, if indicated, are recommended in patients with new-onset or persistent heart failure/shock after fibrinolysis.</i> | I | A |
| <i>Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.</i> | I | A |

- **Technical aspects of invasive strategies:**

| Table 7-5: ESC Recommendations for technical aspects in primary PCI: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Radial access is recommended as the standard approach, unless there are overriding procedural considerations.</i> | I | A |
| <i>PCI with stent deployment in the IRA during the index procedure is recommended in patients undergoing PPCI.</i> | I | A |
| <i>Drug-eluting stents are recommended in preference to bare metal stents in all cases.</i> | I | A |
| <i>In patients with spontaneous coronary artery dissection, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.</i> | I | C |
| <i>Intravascular imaging should be considered to guide PCI.</i> | IIa | A |

| | | |
|--|------------|----------|
| <i>Intravascular imaging (preferably optical coherence tomography) may be considered in patients with ambiguous culprit lesions.</i> | IIb | C |
| <i>Coronary artery bypass grafting should be considered in patients with an occluded IRA when PPCI is not feasible/unsuccessful and there is a large area of myocardium in jeopardy.</i> | IIa | C |
| <i>Routine use of thrombus aspiration is not recommended.</i> | III | A |
| Non-IRA strategy: | | |
| <i>Complete revascularization is recommended either during the index PCI procedure <u>or</u> within 45 days.</i> | I | A |

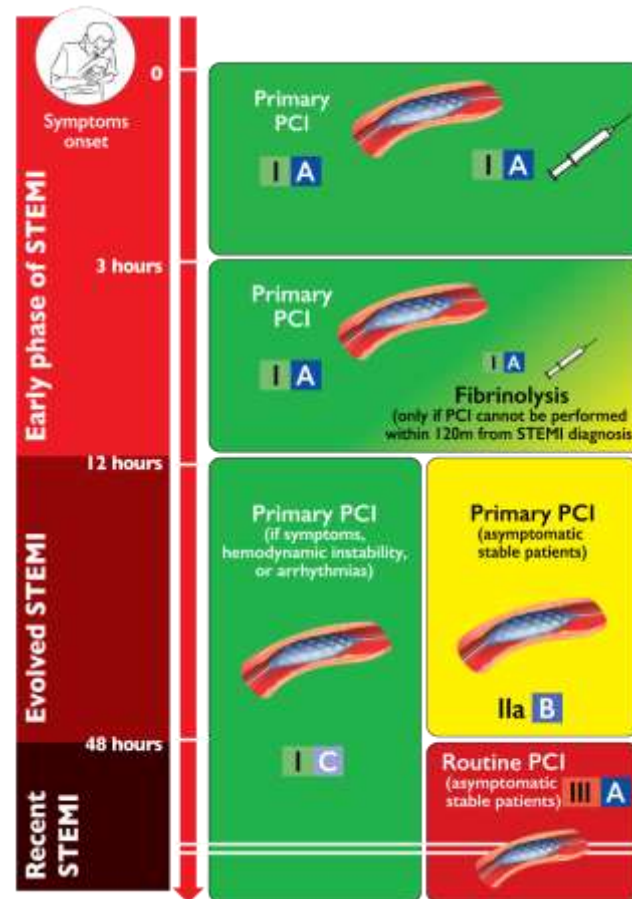


Figure 7-2: Reperfusion strategies in the infarct-related artery according to time from symptoms onset. In early presenters (i.e. those with STEMI diagnosis within 3 hours from symptoms onset), a primary PCI strategy is the reperfusion strategy of choice. If the anticipated time from STEMI diagnosis to PCI-mediated reperfusion is > 120 min, then immediate fibrinolysis is indicated. After 3 hours (and up to 12 hours) of symptoms onset, the later the patient presents, the more consideration should be given to a primary PCI strategy as opposed to administering fibrinolytic therapy. In evolved STEMI (12–48 hours after symptoms onset), a routine primary PCI strategy (urgent angiography and subsequent PCI if indicated) should be considered in all patients. After 48 hours (recent STEMI) angiography should be performed but routine PCI of a total occluded IRA is not recommended. Regardless of the time from symptoms onset, the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or lifethreatening arrhythmias is an indication for a primary PCI strategy. **Source:** 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment

- **Primary PCI and adjunctive therapy:** *For doses revise chapter: Antithrombotic therapy in IHD*

| Table 7-6: ESC recommendations for Periprocedural pharmacotherapy in primary PCI: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Antiplatelet therapy: | | |
| <i>Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.) and an MD of 75–100 mg o.d. for long-term treatment.</i> | I | A |
| <i>Pre-treatment with a P2Y₁₂ receptor inhibitor may be considered in patients undergoing a primary PCI strategy.</i> | IIb | B |
| <i>GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.</i> | IIa | C |
| <i>Cangrelor may be considered in patients who have not received P2Y₁₂ receptor inhibitors.</i> | IIb | A |
| Anticoagulant therapy: | | |
| <i>Parenteral anticoagulation is recommended for all patients with ACS at the time of diagnosis.</i> | I | A |
| <i>Routine use of a UFH bolus (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg) is recommended in patients undergoing PCI.</i> | I | C |
| <i>In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.</i> | I | C |
| <i>Intravenous enoxaparin at the time of PCI should be considered in patients pre-treated with subcutaneous enoxaparin.</i> | IIa | B |
| <i>Routine use of enoxaparin i.v. should be considered.</i> | IIa | A |
| <i>Routine use of bivalirudin should be considered.</i> | IIa | A |
| <i>Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.</i> | IIa | C |
| <i>Fondaparinux is not recommended for primary PCI.</i> | III | B |

- **Fibrinolysis and pharmacoinvasive strategy:**

| Table 7-7: ESC Recommendation on fibrinolysis and adjunctive therapy: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting (aim for target of < 10 min to lytic bolus).</i> | I | A |
| <i>A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.</i> | I | B |
| <i>A half-dose of tenecteplase should be considered in patients > 75 years of age.</i> | IIa | B |
| Antiplatelet co-therapy with fibrinolysis: | | |
| <i>Aspirin and clopidogrel are recommended.</i> | I | A |
| Anticoagulation co-therapy with fibrinolysis: | | |
| <i>Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days.</i> | I | A |
| <i>The anticoagulant can be:</i> | I | A |
| <i>- Enoxaparin i.v. followed by s.c. (preferred over UFH).</i> | I | B |
| <i>- When enoxaparin is not available, UFH given as a weight-adjusted i.v. bolus followed by infusion.</i> | IIa | B |
| <i>- In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.</i> | | |
| Transfer after fibrinolysis: | | |
| <i>Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.</i> | I | A |
| Interventions following fibrinolysis: | | |

| | | |
|--|----------|----------|
| <i>Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.</i> | I | A |
| <i>Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.</i> | I | A |
| <i>Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.</i> | I | A |
| <i>Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.</i> | I | B |

Table 7-8: Doses of fibrinolytic agents and antithrombotic co-therapies:

| Fibrinolytic: | |
|----------------------|--|
| Streptokinase | <i>1.5 million units over 30-60 min I.V</i> |
| Alteplase | <i>15 mg I.V bolus 0.75 mg/kg I.V over 30 min. (up to 50 mg) then 0.5 mg/kg I.V over 60 min. (up to 35 mg)</i> |
| Reteplase | <i>10 units + 10 units I.V bolus given 30 min apart.</i> |
| Tenecteplase | <i>Single I.V bolus: - If BW < 60 kg: 30 mg (6000 IU) - If BW 60:70 kg: 35 mg (7000 IU) - If BW 70:80 kg: 40 mg (8000 IU) - If BW 80:90 kg: 45 mg (9000 IU) - If BW ≥ 90 kg: 50 mg (10000 IU)</i> |

| | |
|--------------------------------|--|
| | <i>It is recommended to half the dose in patients ≥ 75 years of age.</i> |
| Antiplatelet therapies: | |
| Aspirin | <i>Starting dose of 150-300 mg orally (or 75-250 mg I.V if oral ingestion is not possible), followed by a maintenance dose of 75-100 mg/day.</i> |
| Clopidogrel | <i>Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥ 75 years of age: loading dose of 75 mg, followed by maintenance of 75 mg/day.</i> |

- **Coronary Artery Bypass Graft surgery (CABG):**

- CABG should be considered for patients with a patent IRA but with unsuitable anatomy for PCI, and either a large myocardial area at jeopardy or with cardiogenic shock.
- In patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair.
- Patients with haemodynamic deterioration or who are at high risk of recurrent ischaemic events (i.e. patients with a large area of myocardium at jeopardy due to critical coronary stenoses or recurrent ischaemia) should be operated on as soon as possible without waiting for the full recovery of platelet function following discontinuation of DAPT.
- For all other patients, a waiting period of 3–7 days may be the best compromise (at least 3 days following interruption of ticagrelor, 5 days for clopidogrel, and 7 days for prasugrel), while it is recommended that aspirin is continued.
- The first aspirin administration post-CABG is recommended 6–24 h after surgery in the absence of ongoing bleeding events.

Management during hospitalization and at discharge:

| Table 7-9: ESC recommendations for Logistical issues for hospital stay: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>It is indicated that all hospitals participating in the care of STEMI patients have a CCU/ICCU equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.</i> | I | C |
| Transfer back to a referring non-PCI hospital: | | |
| <i>Same day transfer should be considered appropriate in selected patients after successful primary PCI, i.e. those without ongoing myocardial ischaemia, arrhythmia, or haemodynamic instability, not requiring vasoactive or mechanical support, and not needing further early revascularization.</i> | IIa | C |
| Monitoring: | | |
| <i>It is indicated that all STEMI patients have ECG monitoring for a minimum of 24 h.</i> | I | C |
| Length of stay in the CCU: | | |
| <i>It is indicated that patients with successful reperfusion therapy and an uncomplicated clinical course are kept in the CCU/ICCU for a minimum of 24 h whenever possible, after which they may be moved to a step-down monitored bed for an additional 24–48 h.</i> | I | C |
| Hospital discharge: | | |
| <i>Early discharge (within 48–72 h) should be considered appropriate in selected low-risk patients ⁽¹⁾ if early rehabilitation and adequate follow-up are arranged.</i> | IIa | A |

(1) For example, PAMI-II criteria: age < 70, LVEF > 45%, one- or two-vessel disease, successful PCI and no persistent arrhythmias.

Special patient subsets:

▪ **Patients with multivessel disease:**

○ **Management of multivessel disease in ACS complicated by cardiogenic shock:**

Cardiogenic shock may occur in 4-11% of ACS patients. Nearly 80% of ACS patients with CS have MVD.

Immediate coronary angiography, and PCI if feasible, is recommended in patients with acute MI complicated by CS. PCI during the index procedure should be restricted to the IRA only (CULPRIT-SHOCK trial) ⁽¹⁾.

In patients with coronary anatomy unsuitable for PCI, emergency CABG is recommended (Better 6-month survival; SHOCK trial).

○ **Patients with multivessel coronary artery disease undergoing primary PCI:**

Multivessel disease is evident in approximately 50% of patients undergoing PPCI. complete revascularization is recommended in patients with STEMI and MVD (reduced composite of CV death or new MI compared with IRA-only PCI).

○ **Timing of non-IRA revascularization in ACS:** No recommendation in favour of an immediate vs. a staged (i.e. either during index hospitalization or within 45 days of discharge) non-IRA PCI strategy can be formulated (No randomized trials).

○ **Evaluation of non-IRA stenosis severity (angiography vs. physiology):**

Microvascular constriction may also occur in the non-IRAs, leading to overestimation of the severity of non-IRA lesions during the PPCI procedure. Therefore, Functional invasive evaluation of non-IRA severity during the index procedure may be considered.

Table 7-10: ESC Recommendations for management of patients with ACS and multivessel diseases:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>It is recommended to base the revascularization strategy (IRA PCI, multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease</i> | I | B |

(1) In the CULPRIT-SHOCK trial, IRA-only PCI was associated with a significant reduction in all-cause death or renal replacement therapy at 30-day follow-up. At 1-year follow-up, mortality did not differ significantly between the two groups.

| | | |
|--|------------|----------|
| <i>complexity, according to the principles of management of myocardial revascularization.</i> | | |
| Multivessel disease in ACS patients presenting in cardiogenic shock | | |
| <i>IRA-only PCI during the index procedure is recommended.</i> | I | B |
| <i>Staged PCI of non-IRA should be considered (based on ischaemia, symptoms, patient comorbidities, and clinical condition.)</i> | IIa | C |
| Multivessel disease in haemodynamically stable STEMI patients undergoing PPCI: | | |
| <i>Complete revascularization is recommended either during the index PCI procedure or within 45 days.</i> | I | A |
| <i>It is recommended that PCI of the non-IRA is based on angiographic severity.</i> | I | B |
| <i>Invasive epicardial functional assessment of non-culprit segments of the IRA is not recommended during the index procedure.</i> | III | C |

▪ **Patients at high bleeding risk and with blood disorders (anemia and thrombocytopenia):**

- Persistent or worsening anaemia in patients with ACS is associated with an increased risk of recurrent ischaemic events, death, and major bleeding. According to the ARC-HBR, haemoglobin < 11 g/dL at the time of PCI constitutes a major criterion for HBR, whereas haemoglobin between 11 and 13 g/dL (12 g/dL for women) is a minor criterion. There is no formal recommendation as to the optimal transfusion strategy (liberal vs. restrictive) in patients with ACS at present ⁽¹⁾.
- Although there are several classifications to grade the severity of thrombocytopenia, clinically relevant thrombocytopenia can be defined as a platelet count < 100 000/μL or a relative drop in platelet count of 50% from baseline in the context of ACS.

(1) Liberal blood transfusion strategy has been defined as any RBCs transfusion at a Hb level < 9-10 g/ dL, while a Restrictive blood transfusion strategy has been defined as any transfusion at a Hb level < 7-8 g/dL.

Thrombocytopaenia increases the risk of death, major bleeding events, and life-threatening thrombotic events. The ARC-HBR criteria define a platelet count < 100 000/μL as a major criterion for HBR.

- **Pregnancy:** Pregnant women with STEMI should not be managed differently to non-pregnant women. Given the high mortality associated with STEMI in pregnancy, PPCI is the preferred reperfusion therapy. Delivery should be ideally postponed for at least 2 weeks post-ACS as there is increased risk of maternal mortality during this time. It has been demonstrated that SCAD is the most common cause of AMI in pregnancy, and this tends to occur mainly in the late pregnancy or early post-partum periods.
- **Non-reperfused patients:** Patients who fail to receive reperfusion therapy within the recommended time (first 12 h) should immediately be evaluated clinically to rule out the presence of clinical haemodynamic, or electrical instability.
- A primary PCI strategy is indicated in the presence of signs or symptoms suggestive of ongoing myocardial ischaemia, HF, haemodynamic instability, or life-threatening arrhythmias, and should be considered in stable asymptomatic patients between 12-48 h after symptom onset.
- After that time, either a non-invasive test for the presence of residual myocardial ischaemia/viability to decide a late invasive strategy or elective coronary angiography should be considered. However, routine PCI is not indicated in totally occluded IRA beyond the first 48h from symptom onset due to the increased risk of late complications.
- Early echocardiography with LVEF assessment is indicated in all patients.
- In patients in whom PCI is finally performed, ticagrelor or prasugrel are preferred, while in patients who do not undergo PCI, clopidogrel is indicated.
- Anticoagulation, preferably with fondaparinux, is indicated until coronary revascularisation is done or hospital discharge.

| Table 7-11: ESC recommendations for acute coronary syndrome comorbid conditions: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Renal dysfunction: | | |

| | | |
|--|-----|---|
| Moderate to severe CKD (stages III–V) is present in more than 30% of ACS patients. Patients with ACS and concomitant CKD receive less interventional and pharmacological treatment and have a worse prognosis. | | |
| <i>The use of low- or iso-osmolar contrast media (at the lowest possible volume) is recommended for invasive strategies.</i> | I | A |
| <i>It is recommended to assess kidney function using eGFR in all patients with ACS</i> | I | C |
| <i>It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as in patients with normal kidney function.</i> | I | C |
| <i>Hydration during and after angiography should be considered in patients at risk of contrast-induced nephropathy, especially in patients with acute kidney injury and/or CKD with eGFR <30 mL/min/ 1.73 m².</i> | IIa | B |
| Diabetes: | | |
| ACS patients with DM may more commonly present with non-specific symptoms, which can lead to delays in both diagnosis and access to treatment. Both treatment in the acute phase and risk factor management post-ACS is poorer in patients with DM and these patients tend to have more advanced CAD at diagnosis. These factors likely contribute to the worse long-term prognosis associated with ACS in patients with DM, particularly in patients requiring insulin treatment. | | |
| <i>It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.</i> | I | B |
| <i>It is recommended to frequently monitor blood glucose levels in patients with known diabetes mellitus or hyperglycaemia (defined as glucose levels ≥ 11.1 mmol/L or ≥ 200 mg/dL).</i> | I | C |

| | | |
|--|------------|----------|
| <i>It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, CKD, and obesity.</i> | I | A |
| <i>Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.</i> | IIa | C |
| Older adults: | | |
| Owing to the ageing of the population, a higher proportion of elderly patients is expected to present with STEMI. As these patients may present with atypical symptoms, the diagnosis of MI may be delayed or missed. Elderly patients are also at particular risk of bleeding and higher risk of mechanical complications. PPCI has drastically improved outcomes for all ages. | | |
| <i>It is recommended to apply the same diagnostic and treatment strategies in older patients as in younger patients.</i> | I | B |
| <i>It is recommended to adapt the choice and dosage of antithrombotic agent, as well as of secondary prevention medications, to renal function, co-medications, comorbidities, frailty, cognitive function, and specific contraindications.</i> | I | B |
| <i>For frail older patients with comorbidities, a holistic approach is recommended to individualize interventional and pharmacological treatments after careful evaluation of the risks and benefits.</i> | I | B |
| Patients with cancer: | | |
| <i>An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥ 6 months.</i> | I | B |

| | | |
|---|------------|----------|
| <i>A temporary interruption of cancer therapy is recommended in patients in whom the cancer therapy is suspected to be a contributing cause of ACS ⁽¹⁾.</i> | I | C |
| <i>A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis ⁽²⁾ (i.e. with expected survival <6 months) and/or very high bleeding risk.</i> | IIa | C |
| <i>Aspirin is not recommended in cancer patients with a platelet count < 10 000/μL.</i> | III | C |
| <i>Clopidogrel is not recommended in cancer patients with a platelet count < 30 000/μL.</i> | III | C |
| <i>In ACS patients with cancer and < 50 000/μL platelet count, prasugrel or ticagrelor are not recommended.</i> | III | C |

Risk assessment:

▪ Clinical risk assessment:

- **Early assessment of short-term risk:** All patients with STEMI should have an early assessment of short-term risk, including an evaluation of the extent of myocardial damage, the occurrence of successful reperfusion, and the presence of clinical markers of high risk of further events including: older age, fast heart rate, hypotension, Killip class > I, anterior MI, previous MI, elevated initial serum creatinine, history of heart failure, or PAD. *The Global Registry of Acute Coronary Events (GRACE) risk score is recommended for risk assessment.*
- **Evaluation of long-term risk before discharge:** All patients should have an evaluation of long-term risk before discharge, including LVEF, severity of CAD and completeness of coronary revascularization, residual ischaemia, occurrence of

(1) Anticancer drugs associated with high risk of ACS (very common [$> 10\%$]) include: capecitabine, paclitaxel, cisplatin, carfilzomib, bevacizumab, ramucirumab, aflibercept, axitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, ponatinib, and erlotinib.

(2) Related to advanced cancer stage and/or severe irreversible non-CV comorbidities.

complications during hospitalization, and levels of metabolic risk markers, including total cholesterol, LDL-C, HDL-C, fasting triglycerides ⁽¹⁾, and plasma glucose, as well as renal function.

▪ **Non-invasive imaging in management and risk stratification:**

- LV dysfunction is a key prognostic factor for patients with ACS. Routine echocardiography after PPCI is recommended to assess resting LV, RV, and valvular function. In addition, echocardiography can be used to exclude early post-infarction mechanical complications and LV thrombus.
- In patients presenting days after an acute ACS event with a completed MI, the presence of recurrent angina or documented ischaemia and proven viability in a large myocardial territory may help to guide the strategy of planned revascularization of an occluded IRA.
- In patients with a pre-discharge LVEF of $\leq 40\%$, re-evaluation of the LVEF 6-12 weeks after complete revascularization and optimal medical therapy is recommended to assess the potential need for primary prevention ICD implantation.
- Additional parameters, that are measured by imaging, are predictors of both long-term mortality and HF in STEMI survivors. These parameters include: **(1)** infarct size (CMR, SPECT, and positron emission tomography); **(2)** MVO (CMR); and **(3)** intra-myocardial haemorrhage (CMR).

| Table 7-12: Summary of indications for imaging and stress testing in STEMI: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| At presentation | | |
| Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography. | I | C |
| Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain. | IIa | C |

(1) As LDL-C tend to decrease during the first days after MI, they should be measured as soon as possible.

| | | |
|---|------------|----------|
| <i>Routine echocardiography that delays emergency angiography is not recommended.</i> | III | C |
| <i>Coronary CT angiography is not recommended.</i> | III | C |
| During hospital stay (after primary PCI) | | |
| <i>Routine echocardiography is recommended during hospitalization to assess regional and global LV function, detect mechanical complications, and exclude LV thrombus.</i> | I | C |
| <i>Emergency echocardiography is indicated in haemodynamically unstable patients.</i> | I | C |
| <i>When echocardiography is suboptimal/inconclusive, CMR imaging may be considered.</i> | IIb | C |
| After discharge | | |
| <i>In patients with pre-discharge LVEF ≤ 40%, repeat echocardiography 6–12 weeks after MI, and after complete revascularization and optimal medical therapy, is recommended to assess the potential need for primary prevention ICD implantation.</i> | I | C |
| <i>When echo is suboptimal or inconclusive, alternative imaging methods (CMR preferably) should be considered to assess LV function.</i> | IIa | C |

Long-term therapies for STEMI:

Table 7-13: ESC Recommendations for long-term management after ACS:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Cardiac rehabilitation: | | |
| <i>It is recommended that all ACS patients participate in a medically supervised, structured, comprehensive, multidisciplinary exercise-based cardiac rehabilitation and prevention programme.</i> | I | A |
| Lifestyle management: | | |
| <i>It is recommended that ACS patients adopt a healthy lifestyle, including:</i> | I | B |

| | | |
|---|------------|----------|
| <ul style="list-style-type: none"> - Stopping all smoking of tobacco ⁽¹⁾ - Healthy diet (Mediterranean style) - Alcohol restriction (max. 100 g/week; same limit for men and women). - Regular aerobic physical activity and resistance exercise - Reduced sedentary time | | |
| In smokers, offering follow-up support, nicotine replacement therapy, varenicline or bupropion, individually or in combination, should be considered ⁽²⁾ . | IIa | A |
| Lipid-lowering drugs: | | |
| Statin therapy should be started during ACS hospitalization regardless of the baseline LDL. Statin's benefit is not usually immediate but may become evident within 1 month. A more immediate benefit is seen in patients undergoing PCI, as high-dose statin reduces peri-PCI MI. Note that, for patients receiving chronic statin therapy, the harm from statin withdrawal is immediate, with an early cardiac risk that is higher than that of statin non-users. | | |
| It is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values. | I | A |
| It is recommended to aim to achieve an LDL-C level of < 55 mg/dL (< 1.4 mmol/L) and to reduce LDL-C by ≥ 50% from baseline. | I | A |
| If the LDL-C goal is not achieved despite maximally tolerated statin therapy after 4-6 weeks, the addition of ezetimibe is recommended. | I | B |

-
- (1)** Tobacco abstinence is associated with a reduced risk of re-infarction (30-40%) and death (35-45%) after ACS. Interventions for smoking cessation should begin during hospitalization using a combination of behavioural interventions, pharmacotherapy, and counselling. An average weight gain of 5 kg can be expected when a person quits smoking, but it is important to recognize that the CV risk from continued smoking outweighs the CV risk from gaining weight.
- (2)** Drug interventions, including nicotine-replacement therapy (NRT), bupropion and varenicline, should be considered along with behavioural support. All forms of NRT are effective, and the anti-depressant bupropion aids in long-term smoking cessation with similar efficacy to NRT. Varenicline is the most effective medical treatment to support smoking cessation and is safe in ACS patients.

| | | |
|--|------------|----------|
| <i>If the LDL-C goal is not achieved despite maximally tolerated statin therapy and ezetimibe after 4-6 weeks, the addition of a PCSK9 inhibitor is recommended.</i> | I | A |
| <i>It is recommended to intensify lipid-lowering therapy ⁽¹⁾ during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission.</i> | I | C |
| <i>For patients with a recurrent atherothrombotic event (recurrence within 2 years of first ACS episode) while taking maximally tolerated statin-based therapy, an LDL-C goal of < 40 mg/dL (< 1.0 mmol/L) may be considered.</i> | IIb | B |
| <i>Combination therapy with high-dose statin plus ezetimibe may be considered during index hospitalization.</i> | IIb | B |
| RAAS system inhibitors: | | |
| <ul style="list-style-type: none"> ○ ACE inhibitors have been demonstrated to improve outcomes in post-MI patients with additional conditions, such as clinical HF and/or LVEF ≤ 40%, diabetes, CKD, and/or hypertension. ○ MRAs reduce short-term (30 days) and long-term mortality when initiated in MI patients with EF < 40%, at 3-7 days (EPHESUS trial). However, its acute initiation in the emergency department in MI with EF > 40% was not beneficial (ALBATROSS trial). | | |
| <i>ACE inhibitors (ARBs in case of intolerance) are recommended in ACS patients with HF symptoms, LVEF ≤ 40%, diabetes, hypertension, and/ or CKD.</i> | I | A |
| <i>Mineralocorticoid receptor antagonists are recommended in ACS patients with an LVEF ≤ 40% and HF or diabetes.</i> | I | A |
| <i>Routine ACE inhibitors for all ACS patients regardless of LVEF should be considered.</i> | IIa | A |
| Beta-blockers: | | |
| <i>The clinical benefit of β-blockers after ACS in patients with reduced LVEF is supported by evidence from contemporary trials. However, the evidence for prescribing β-blockers after uncomplicated ACS in patients with LVEF > 40% is less well established. β-blockers significantly reduced the endpoint of death/MI/cardiac arrest between day 2 and day 15, but increased this endpoint in the first day and in unstable patients, making the overall β-blocker effect neutral (COMMIT-CCS trial). Therefore, β-blockers</i> | | |

(1) Increase statin potency/dose if the patient was on low-potency/low-dose statin, add ezetimibe if the patient was only on statins at highest tolerated dose, or add PCSK9 inhibitor if the patient was on statins plus ezetimibe.

| | | |
|---|------------|----------|
| <i>should be avoided on the first day if there are any HF signs or features predictive of cardiogenic shock: SBP < 120 mmHg, heart rate > 110 bpm, or age > 70 years.</i> | | |
| <i>Beta-blockers are recommended in ACS patients with LVEF ≤ 40% regardless of HF symptoms.</i> | I | A |
| <i>Routine beta-blockers for all ACS patients regardless of LVEF should be considered.</i> | IIa | B |
| Proton pump inhibitors: | | |
| <i>Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds.</i> | I | A |
| Vaccination | | |
| <i>Influenza vaccination is recommended for all ACS patients.</i> | I | A |
| Anti-inflammatory drugs: | | |
| <i>Low-dose colchicine (0.5 mg once daily) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent CV disease events occur under optimal therapy.</i> | IIb | A |

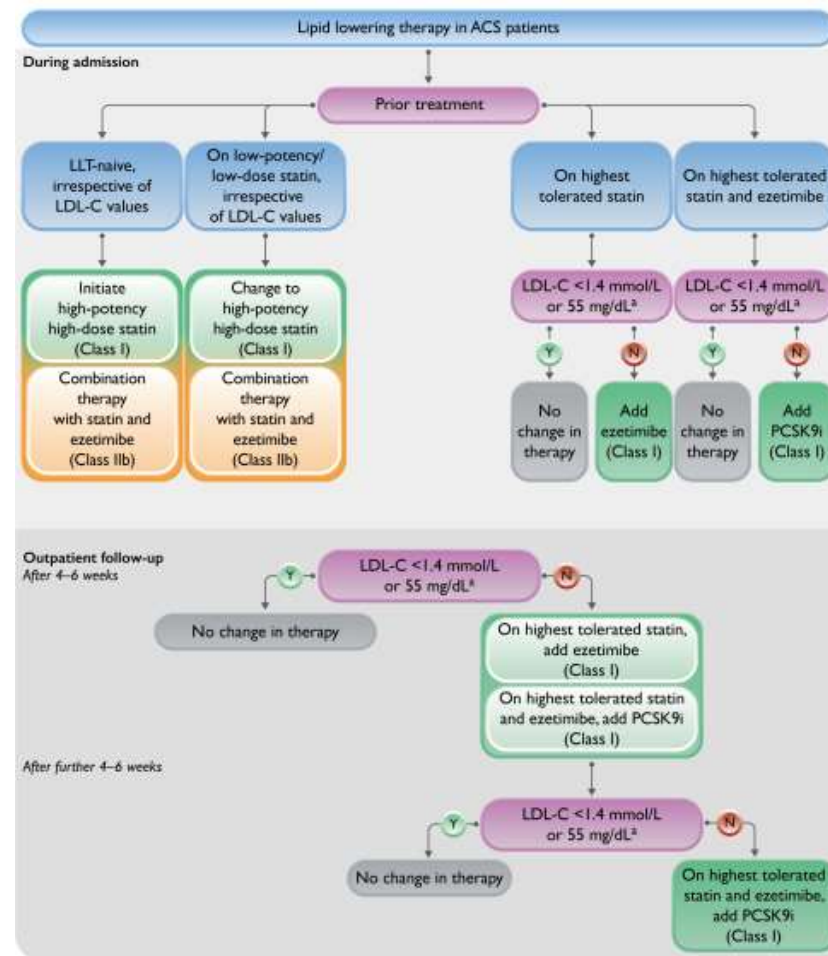


Figure 7-3: Lipid-lowering therapy in ACS patients. A) Consider LDL-C < 40 mg/dl (1.0 mmol/L) if recurrent event. **Source:** 2023 ESC Guidelines for the management of acute coronary syndrome.

Complications following ACS ⁽¹⁾:

Acute heart failure

- In acute MI, pulmonary edema results from volume redistribution to the lungs without overt volume overload and sometimes without LV dilatation. Treatment consists of small doses of furosemide (e.g., 20-40 mg IV), along with a low dose of intravenous NTG to reduce preload. *Excessive preload or afterload reduction may, however, precipitate shock.*
- Patients presenting with acute HF (including patients with CS) complicating ACS require immediate ICA.
- These patients should also undergo emergency echocardiography/chest ultrasonography to gather information about LV and RV function, regional wall motion abnormalities, valvular function, and possible mechanical complications.

Cardiogenic shock

Cardiogenic shock occurs in 4–7% of STEMI (vs. 2.5% of NSTEMI). It is occasionally present on admission, and more typically develops soon after admission, at a median of 5.5 hours after MI onset (vs. a later shock development, at ~3 days, in NSTEMI with three-vessel disease).

- **Pathophysiology in MI:** Beside systolic dysfunction, several mechanisms explain cardiogenic shock in MI:
 - Half of patients with cardiogenic shock have a small or normal-size LV, which represents failure of the mechanism of acute LV dilatation to increase stroke volume.
 - For a given LV contractility, the more severe impairment of LV compliance in acute MI leads to a more severe rise of LV filling pressure, which further reduces coronary perfusion pressure.
 - Transient hypotension (drugs, arrhythmia, sedation) in an initially stable patient may transiently reduce coronary blood flow and thus initiate a vicious circle of progressive myocardial ischemia that sustains the hypotension. *β -blockers, ACE-Is, and other vasodilators, including sedatives administered during PCI or during intubation, may precipitate shock in a pre-shock patient who*

(1) These complications may occur in all cases of ACS, much more common in STEMI than NSTEMI-ACS.

depends on the compensatory vasoconstriction and tachycardia. This partly explains why cardiogenic shock often develops after hospital admission.

- Aggressive diuresis may precipitate shock in MI since the pulmonary edema of MI results from volume redistribution rather than florid volume overload.
- In over 25% of MI-associated cardiogenic shock, SVR is inappropriately low or normal rather than elevated. *This mismatch between myocardial depression and inappropriate vasodilatation (or lack of compensatory vasoconstriction) may result in cardiogenic shock.*

This inappropriate vasodilatation is initiated by a systemic inflammatory response syndrome (SIRS) secondary to MI early on, then a septic process may develop later on (bacterial translocation?). High levels of cytokines and *inducible* nitric oxide synthase, beyond the healthy levels of *endothelial* nitric oxide synthase, precipitate vasodilatation and further myocardial depression. Also, PCI may initiate a reperfusion injury with further activation of inducible nitric oxide synthase, and thus vasodilatation and myocardial depression. This is a temporary phenomenon, as the benefit from PCI eventually takes over.

○ **Differential diagnosis:**

- **RV infarct:** RV-related shock should be considered **whenever hypotension occurs in inferior MI**. RV infarct occurs in 30% of inferior MIs, mainly with proximal RCA occlusion. Only one-half of RV infarcts produce clinical RV failure.
- **Mechanical complications** (mitral regurgitation, ventricular septal rupture, free wall rupture) or **tamponade**.
- **Arrhythmias** (inappropriate bradycardia, advanced AV block, VT).
- **Vagal stimulation and vagal shock** in inferior MI. It manifests as bradycardia with clear lungs and low JVP. It is treated with atropine and fluid administration.
- **Hypovolemic hypotension:** hypotension with clear lungs, low JVP, and no bradycardia. May attempt small fluid challenge in this situation.

RV-related cardiogenic shock

- Acutely, RV shock is associated with a very high mortality, almost similar to LV shock (~50%), despite a younger age, a higher LVEF, and a much lower likelihood of three-vessel CAD.

- Reperfusion promptly improves RV function within 1 hour and normalizes it within 3–5 days, dramatically improving the survival and the clinical status. Non-reperfused patients continue to have a poor RV function and poor hemodynamics at 3–5 days; RV function eventually normalizes within 1 month. RV is thin (less oxygen demands), easily recruits collaterals because of its lower coronary microvascular resistance, and has a capacity to derive oxygen from the RV cavity through the deep trabeculations; thus, RV usually recovers most of its contractile function.
- PCWP may be equally elevated in RV shock as in LV shock. This is mainly related to the RV–LV interdependence. The dilated RV pushes the septum, forcing the LV diastolic pressure to equalize with the RV diastolic pressure and reducing LV output.
- The usual culprit of RV shock is RCA in 96% of cases, usually proximal RCA affecting flow to the acute marginal branches (RV free wall) and the PDA (inferior septum). The left coronary is responsible for RV infarction in 4% of cases; when the left coronary supplies collaterals to a chronically occluded RCA.
- **Treatment of RV shock (beside emergent reperfusion):**
 - **Fluid administration.** In patients without significant pulmonary hypertension, one may increase the RA pressure to passively force flow through the PA and therefore increase the cardiac output. However, this is only effective as long as the RV does not dilate. Once the RV dilates, fluid administration worsens ventricular interdependence, further reduces LV output, and increases TR. Thus, 500 ml fluid boluses are provided while assessing the hemodynamic response, and preferably while checking RV size on TTE.
 - **Inotropes/vasopressors.** After RV preload has been optimized, the patient with persistent hypotension is treated with inotropes/vasopressors. Since at least half of the RV coronary flow occurs in systole, RV coronary flow depends on the driving gradient between SBP and RV systolic pressure.
 - **Maintenance of AV synchrony** is critical in acute RV failure, as the RV but also the underfilled LV are dependent on the extra-filling provided by the atrial contraction, more so than a failing, overfilled LV.
AF may need to be DC cardioverted. Patients with AV block or AV dissociation from an accelerated junctional rhythm need to have atrial and ventricular sequential pacing. Transvenous atrial and ventricular leads are placed through separate venous accesses (e.g., bilateral femoral accesses).

As in any shock, “normal” heart rate of 60-70 bpm is inappropriate and dictates pacing to rate > 80 bpm.

- **Hypoxemia** should be aggressively treated as hypoxemia increases PVR and RV afterload.
- **IABP** may be useful to increase flow across the reperfused RCA. It is more definitely indicated when concomitant LV failure is present (pulmonary edema).
- **Inhaled NO** has shown to reduce RA pressure and PVR, and increase stroke volume, in RV MI.

Mechanical complications

[Within the first 14 days of MI with 2 peaks (1 and 3–5 days)]

Mechanical complications occur in 0.27% of STEMI cases and 0.06% of NSTEMI cases, with in-hospital mortality rates of 42.4% and 18%, respectively. They are responsible for 12% of cases of cardiogenic shock (severe MR, 7%; VSR, 3.9%).

Clinical features: Sudden hypotension, the recurrence of chest pain, new cardiac murmurs suggestive of acute mitral regurgitation or a ventricular septal defect, pulmonary congestion, or jugular vein distension should raise suspicion of a mechanical complication. Immediate echocardiographic assessment is indicated when mechanical complications are suspected.

• **Severe mitral regurgitation (MR):**

○ **Mechanism:**

- **Posterior leaflet tethering** – A degree of ischemic MR is seen in ~30% of acute MI.

Inferior MI with localized inferior/posterior akinesis pulls the posterior papillary muscle posterolaterally, with subsequent tethering of the posterior mitral leaflet (predominantly). Tethering may also occur with anterior MI and is usually a posterior tethering due to global LV dilatation.

- **Papillary muscle rupture:** usually the posterior papillary muscle in the context of *inferior or posterior MI*. The posterior papillary muscle is supplied by one artery, the PDA (from a dominant RCA or LCx), whereas the anterolateral muscle has a dual blood supply from the LAD (usually first diagonal) and the LCx. Papillary muscle rupture occurs in ~1% of MIs.

- **Diagnosis:** The murmur may be faint or absent with acute MR, because of the near-equalization of LV and LA pressures. Echo distinguishes papillary muscle rupture (treated surgically) from leaflet tethering (initially treated with revascularization and

supportive measures). In the former, the leaflet(s) are flail, prolapsed, with flailing of chordae and flailing of an echogenic piece of papillary muscle; in the latter, the posterior leaflet is restricted and the jet is usually posterior.

Note that, TTE may miss severe acute MR because of the narrowing of the pressure difference between the LV and LA, leading to attenuation of the regurgitant color flow.

- **Treatment:**

Place IABP and administer IV vasodilators in all cases of acute severe MR.

Papillary muscle rupture dictates emergent valvular surgery + CABG. MV replacement is most often performed as it is more expeditious than repair.

When severe acute MR is secondary to acute mitral leaflet tethering, the patient may be treated with percutaneous revascularization, vasodilators and temporary IABP support. It is expected that leaflet tethering improves once the function of the reperfused territory improves. Surgery should be considered a second-line therapy if no improvement with medical therapy.

- **Ventricular septal rupture (VSR):** [~1% of MIs (only 0.2% of reperfused MIs)].

Anterior MI (LAD) and inferior MI (mainly RCA) were equally common causes of VSR in the SHOCK registry, while other registries suggest that anterior MI is slightly more common. The location is apical septal in anterior MI and basal inferior in inferior MI. VSR leads to a severe left-to-right shunting with severe hypotension and LV volume overload. The murmur is usually loud in VSR and is associated with a thrill at the left lower sternal border. Pulmonary edema is less marked with VSR than with MR.

- **Treatment:** Emergent surgical repair and Coronary revascularization. The operative mortality is ~50% and is higher in basal-inferior VSR, because the latter is more serpyiginous and often associated with RV infarct. Prepare the patient with IABP/nitroprusside/inotropes.

- **Free wall rupture:**

Occurs in ~2% of MIs and is the most common and most underdiagnosed mechanical complication ($\leq 1.5\%$ of patients treated with PCI, 3% of patients treated with thrombolysis, 6% of patients not reperfused).

The most common location is anterior MI; the second most common location is lateral MI.

Myocardial rupture usually results from the shear stress at the border between the live and the infarcted area. In the reperfusion era, myocardial rupture is most frequently seen in the first 24 hours (SHOCK registry). It may occur at 3–5 days, particularly in non-reperfused patients, when the forming scar thins, expands, and exerts excessive tension at the border. In the second week, the rupture may involve the thin necrotic area itself.

Free wall rupture often leads to tamponade and pulseless electrical activity. It commonly has one of the following prodromes: chest pain, ST segment re-elevation, bradycardia, or syncope from a vagal shock.

TTE may show a pericardial effusion with layered echodensities, corresponding to blood, in free wall rupture; however, it may miss a concealed rupture (an effusion is not seen in 25% of concealed ruptures).

- **Dynamic LVOT obstruction:** [1–2% of MIs and up to 12% of anterior MIs in women].

It is due to anteroapical akinesis associated with a compensatory hyperkinesis of the LV base. This narrows the LVOT and leads to systolic anterior motion (SAM) of the mitral valve, similar to HOCM.

Hypotension and pulmonary edema may subsequently occur. Clinically, a new, dynamic systolic murmur, similar to HOCM murmur, is heard. MR murmur may be heard.

As opposed to the treatment of cardiogenic shock, inotropes, diuretics, and IABP should be avoided, as they worsen the basal hyperkinesis and LVOT narrowing. ***β-Blockers*** are used to reduce the LVOT hyperkinesis. ***α-Agonists*** may be used in case of hypotension.

Recurrent infarction and ischemia

Within 28 days, recurrent infarction or ischemia occurs in ~10–15% of patients treated with fibrinolytic therapy, vs. ~2% of patients treated with PCI.

Recurrent infarction is usually due to reocclusion and is also called “**infarct extension**,” which is different from “**infarct expansion**” (LV remodeling).

It is diagnosed based on clinical grounds, ECG, and a reincrease of a downtrending troponin by > 20%.

- **Treatment:**

- Escalate β -blockers, NTG, and readminister anticoagulants.

- Emergent PCI is indicated in STEMI, refractory angina, or hemodynamic instability. Otherwise, a non-urgent coronary angiogram is usually performed.
- For recurrent ST elevation, the fibrin-specific fibrinolytics may be (re-)administered if PCI cannot be performed in a timely fashion.

Tachyarrhythmias

A. Ventricular arrhythmias:

The risk of out-of-hospital cardiac arrest in STEMI is ~30%, mainly in the first hour after STEMI onset, when over half of all VF episodes occur (risk of VF during the first hour $\geq 12\%$); and between hours 1 and 4, where most of the remaining VF events occur.

Conversely, for patients who make it to the hospital without cardiac arrest, the risk of primary VF within 48 hours is ~4%, and the risk of VT and/or VF is ~10%.

Urgent reperfusion is most important as ischaemia is often the trigger for these arrhythmias. Early administration of i.v. or oral beta-blockers reduces the incidence of malignant arrhythmias. Beta-blockers or amiodarone are recommended if malignant arrhythmias occur and lidocaine may be considered if these are contraindicated.

The prognostic role of early VT/VF within the first 48 h of STEMI is still controversial. Sustained VT/VF late after reperfusion (> 48 h) requires an evaluation for ICD for secondary prevention.

• **VF and sudden death:** There are three types of VF (mostly characterized in fibrinolytic trials):

- **Primary VF:** VF occurring in the first 48 hours after MI without an associated shock or severe HF (Killip class I). It occurs because of rapid potassium fluxes with increased automaticity and dispersion of repolarization, or increased sympathetic or vagal tone. It mostly occurs in the first 4 hours.

Primary VF is associated with a 2–4 times increased in-hospital mortality. However, VF does not affect long-term mortality in survivors.

- **Late VF:** VF occurring after 48 hours without an associated HF or shock. It is secondary to the myocardial scar and correlates with pump failure, extensive myocardial damage, and increased long-term mortality.
- **Secondary VF:** VF occurring in association with HF or shock (< 48 h or > 48 h) and portends a poor early and long-term survival, mainly from a downhill HF course.
- **Sustained VT:** There are two types of VT:
 - **Polymorphic VT** is usually an ischemic rhythm that occurs in the first 48 hours of MI or during ischemic recurrences. In contrast to torsades de pointes, this polymorphic VT is usually associated with a normal or a minimally prolonged QT interval.
 - **Monomorphic VT**, whether occurring early (in the first 48 hours) or late (> 48 hours), is a sign of extensive myocardial damage and portends a strikingly increased in-hospital and long-term mortality. It usually reflects the presence of large substrate in the border zone between viable and infarcted tissue.
- **Non-sustained VT (NSVT):**
 - **Early NSVT** (< 48 hours) is not associated with any impairment of short- or long-term survival.
 - **Late NSVT** is associated with impaired long-term survival.

NSVT does not require any specific therapy; provide general MI therapy especially, β -blocker if possible.

- **Accelerated idioventricular rhythm** = slow wide ventricular rhythm at a rate of 60–100 (120) bpm.

Its incidence is 20% in the first 48 hours, mostly after successful reperfusion. However, it cannot be used as a standalone reperfusion marker. In any case, it is benign and resolves spontaneously; no specific treatment is required.

B. **Accelerated junctional rhythm** (also called non-paroxysmal junctional tachycardia)

The accelerated junctional rhythm is automatic rhythm originating from the AV node at a rate of 70-130 bpm, often ~80 bpm.

The junctional rhythm is faster than the sinus rhythm, causing AV dissociation.

Sometimes, the junctional and sinus rhythms compete at close rates, leading to *isorhythmic AV dissociation*, i.e., some beats may be sinus beats preceded by sinus P waves, while the other beats may be junctional beats dissociated from P waves and showing up at any deceleration of the sinus P rate.

This rhythm may occur with inferior MI, is benign and transient, and does not generally require any specific therapy unless the patient is in shock. In shock, atrial pacing at a rate faster than the junctional rhythm may be performed to promote AV synchrony and a more appropriate rate for shock.

c. Atrial fibrillation, atrial flutter:

AF is the most frequent supraventricular arrhythmia in patients with ACS. It is associated with increased in-hospital as well as long-term mortality, partly related to the associated pump failure and late VT/VF.

Electrical cardioversion is required for AF causing hemodynamic instability.

Adequate rate control can be achieved by administration of beta-blockers depending on the presence of HF and low ejection fraction. For patients with depressed LVEF, amiodarone or digoxin could be used (preferably amiodarone). In cases of hypotension, digoxin is preferred over amiodarone or beta-blockers. Patients with risk factors for thrombo-embolism should receive chronic oral anticoagulation.

Bradyarrhythmias, bundle branch blocks, fascicular blocks ⁽¹⁾

A. Inferior MI:

Complete AV block is seen in ~11% of inferior MIs, mostly on the first day. Complete AV block is associated with a larger MI, more RV MI, and a higher in-hospital mortality.

In the first 24 hours, sinus bradycardia and AV blocks may develop due to increased vagal tone that accompanies inferior MI. Beyond 24 hours, the AV block is due to ischemia and edema of the AV node and is more persistent, but eventually resolves within a few days (< 1 week).

Treatment:

AV block that occurs in the first 24 hours responds to atropine.

Later AV block (> 24 hours) does not typically respond to atropine as it is not driven by a high vagal tone; it only requires temporary transvenous ventricular pacing in case of shock, HF, symptoms of weakness/ dizziness, or complete AV block with a rate < 40 bpm.

B. Anterior MI:

The bundle branches and fascicles are, at least partially, supplied by the LAD. Anterior MI may lead to bundle branch blocks and AV block. The AV block is Hisian or infra-Hisian and is usually preceded by bundle branch blocks.

(1) Note the following arterial supply:

- The sinus nodal artery originates from the proximal RCA (60%) or the LCx (40%).
- The AV nodal artery originates from the AV groove continuation of a dominant RCA (90%) or a dominant LCx (10%).
- The right bundle mainly has a single arterial supply from the LAD (first septal branch).
- The left anterior fascicle has a single arterial supply from the LAD (first septal branch).
- The His bundle, the main left bundle, and the posterior fascicle have a dual supply from the LAD septal branches and the AV nodal artery.

The conduction system is more resistant to ischemia than the myocardium, as the myocardial cells require much more O₂ for their continuous mechanical work than the electrical cells. This explains why conduction blocks are frequently due to edema or ischemia rather than necrosis and are usually reversible (75% of the cases). If not reversible, and if secondary to MI rather than degenerative disease, the myocardial injury is usually quite extensive (e.g., persistent RBBB or LBBB).

A second- or third-degree AV block is seen in ~3.5% of anterior MIs and portends a very high mortality related to pump failure (3–4 times increase in mortality).

Transvenous pacing, while indicated for any high-grade second- or third-degree AV block, even if asymptomatic, does not improve the overall prognosis that is dictated by the pump function.

Permanent pacing is indicated for persistent, infranodal second- or third-degree AV block.

c. **Bundle branch and fascicular blocks:**

Approximately 2–8% of STEMI patients develop some form of new intraventricular block, LAFB being the most common block. Beside the risk of progressing to complete AV block, *a new BBB is independently associated with a two- to six-fold increase in in-hospital mortality, HF, and VF, because it correlates with extensive infarction.*

Approximately 75% of these blocks are transient, and transient blocks do not portend any increase in mortality. Old BBBs do not portend any increase in mortality either. *Both RBBB and LBBB are associated with the same increase in mortality.*

A standby temporary transcutaneous or transvenous pacemaker is indicated for a new BBB or bifascicular block occurring in anterior MI.

LV aneurysm and pseudoaneurysm

A. **LV aneurysm:**

- **Dyskinesis** signifies that a non-contractile myocardial segment moves out during myocardial contraction and moves in during relaxation (paradoxical motion).

LV aneurysm is an extreme form of dyskinesis and consists of a *thin* area of infarcted, dyskinetic myocardium which protrudes in both systole and diastole, forming a separate chamber.

- LV aneurysm usually reflects the presence of extensive transmural necrosis; contrarily, dyskinesis may be seen with acute reversible ischemia, post-ischemic stunning, or takotsubo cardiomyopathy without any necrosis, in which case the myocardial wall is not thin (it may appear thin in systole from the lack of thickening, but it is not thin in diastole).

- Dyskinesis without an aneurysm is much more common than a true aneurysm.
- An aneurysm leads to increased preload and afterload, and a double mortality for the same EF.
- LV aneurysm occurs in 5% of STEMI cases, mainly anteroapical STEMI (80% of LV aneurysms are anteroapical; the rest are inferoposterior).
- LV aneurysm may initiate or worsen: **(i)** HF, **(ii)** angina (from the adverse loading conditions), **(iii)** VT, and **(iv)** mural thrombosis.
- The diagnosis is made by echocardiography. ST elevation that persists > 3 weeks suggests LV aneurysm, but may also be seen with a dyskinetic, often non-viable wall.
- Treatment consists of: HF therapy to reverse LV remodeling. Aneurysmectomy is indicated for refractory HF or refractory VT, mainly in conjunction with CABG. Operative mortality is < 10%.
- The early use of ACE-I, β -blocker, and aggressive blood pressure control prevents LV aneurysm from appearing or expanding.

B. LV pseudoaneurysm:

- Pseudoaneurysm is a myocardial rupture that has been concealed by pericardium, organized thrombus and fibrosis. Unlike a true LV aneurysm, the LV pseudoaneurysmal wall does not contain any myocardium.
- A pseudoaneurysm may also be seen after trauma or cardiac surgery (especially mitral surgery, at the posterobasal level).
- A pseudoaneurysm has a 40–50% risk of progressing to a full rupture, and thus warrants urgent surgical suturing. Conversely, a true aneurysm does not rupture (it may, rarely, rupture in the first 2 weeks of MI, but does not rupture later on, once it is fully fibrosed).
- *On imaging, the distinction between a true LV aneurysm and a pseudoaneurysm is:*
 - Pseudoaneurysm has a narrow neck with a neck-to-internal diameter ratio < 0.5, although occasionally, it can be 0.5–1.
 - Doppler may also support the diagnosis of pseudoaneurysm by showing a to-and-fro turbulent flow through the narrow neck, which corresponds to a murmur on exam. However, echo-Doppler does not always allow this distinction.
 - MRI may be used in equivocal cases and shows loss of epicardial fat across the pseudoaneurysm.

- Left ventriculography is also highly accurate in distinguishing an aneurysm from a pseudoaneurysm. In case of a pseudoaneurysm, it shows a pocket with a contrast stain that persists over multiple beats.

Pericardial complications

A. Acute post-infarction pericarditis:

In the reperfusion era, inflammatory pericarditis occurs in ~5% of STEMIs, usually large or anterior STEMIs. Less commonly, it may occur in large NSTEMIs.

As pericarditis correlates with a larger MI size, it carries worse prognosis despite being innocuous per se.

Over half of pericarditis cases are not associated with any effusion; similarly, half of pericardial effusions are not inflammatory (no rub), and rather result from pump failure and transudation.

- **Diagnosis:** Pericarditis develops in the first few days of MI, most commonly the first or second day, and usually lasts a few days only. The pain is typically pleuritic, and radiation to the trapezius is characteristic. A fleeting rub may be heard.

On ECG, a pattern of diffuse pericarditis with diffuse ST elevation is rare (<20%); rather, pericarditis is localized to the infarcted area with ECG findings of localized ST elevation. *The persistence of upright T waves or the reversal from inverted T waves to upright T waves very early after MI* is 100% sensitive for the diagnosis of pericarditis.

- **Treatment:**

NSAIDs should not be used post-MI because of the risk of adverse LV remodeling and free wall rupture. High-dose aspirin (325–650 mg Q 6–8 h) may be used; alternatively, acetaminophen or colchicine may be used for this transient process.

The risk of hemorrhagic transformation of acute post-MI pericarditis is theoretical and very rarely reported. Thus, pericarditis should not alter the antiplatelet regimen and anticoagulation may be continued in patients who need it, with close monitoring.

B. Pericardial effusion:

- Small pericardial effusions (5–9 mm) are seen in 5% of STEMIs, usually during the first 5 days and slowly resolving over several weeks. It may be secondary to pericarditis or to pump failure.

- A moderate pericardial effusion, even asymptomatic, is associated with an 8% risk of death from free wall rupture. This effusion warrants at least a more prolonged monitoring, close echo surveillance, and potentially a cardiac MRI to diagnose impending rupture. Anticoagulation should be discontinued.
- A large effusion with tamponade or pulseless electrical activity is usually due to free wall rupture and warrants emergent surgical repair.

C. Dressler syndrome or post-cardiac injury syndrome:

This rare syndrome is an inflammatory and likely autoimmune process related to anticardiac antibodies. It occurs 1–8 weeks after MI, and leads to fever, pericarditis, but also pericardial and pleural effusions.

It is treated similarly to early post-MI pericarditis.

LV thrombus and thromboembolic complications

- LV thrombus is most common in patients with anteroapical MI, with a 30-40% incidence in the pre reperfusion era, down to 10% in the thrombolytic era and 5-10% in the PCI era.
- It usually forms in the first week after MI, with at least 25% of thrombi forming in the first 24 hours; however, a few thrombi form 1–3 months later.
- In addition to akinesis, the hypercoagulable state of STEMI promotes the formation of LV thrombi, particularly early LV thrombi. Severe global LV dysfunction is not a prerequisite for LV thrombus.
- In the absence of anticoagulation, LV thrombus is associated with a ~10–15% embolization risk. In one study, all embolic events occurred within 3-4 months of MI.
- Higher embolization rate is observed in: Pedunculated morphology, AF, severe HF, severe LV dysfunction, and older age.
- Echocardiography is usually used for diagnosis. However, echo may give a false positive diagnosis because of side lobe artifacts or reverberations from the ribs. Cardiac MRI is the gold standard for the diagnosis and allows the distinction between thrombus and the underlying myocardial scar.

- **Treatment:** Once an LV thrombus has been diagnosed, OAC therapy (warfarin or NOAC) should be considered for 3–6 months. Warfarin allows intrinsic lysis of the thrombus or, at least, organization and endothelialization. So, it almost abolishes the embolization risk.

Bleeding

Bleeding is associated with a poor prognosis in ACS patients. The mechanisms by which bleeding increases the risk of death are multifactorial. Intracranial or massive haemorrhage directly threatens life through fatal brain damage or sudden cardiocirculatory collapse. Blood transfusion may increase systemic inflammation and represents one of the possible links between bleeding and subsequent mortality. Bleeding is also a major driver of unplanned discontinuation of DAPT and other drugs (e.g. statins, B-blockers).

Early and late mortality after STEMI

- The short-term mortality (30 days) is, on average, 4–5% for patients treated with primary PCI, 6–7% for patients treated with fibrinolytics, and ~11–12% for patients not treated with reperfusion therapy.
- Afterward, the yearly mortality is 2–6% depending on the degree of LV dysfunction, the presence of HF, and the presence and extent of residual ischemia and residual severe CAD.
- Note that NSTEMI has the same short- and long-term mortality as STEMI (but lower in-hospital mortality).

| Table 7-14: ESC recommendations for acute coronary syndrome complications: | | |
|---|------------|----------|
| Recommendations | Class | Level |
| Heart failure | | |
| <i>IABP should be considered in patients with haemodynamic instability/cardiogenic shock due to ACS-related mechanical complications.</i> | Ila | C |
| LV thrombus | | |

| | | |
|--|------------|----------|
| <i>CMR imaging should be considered in patients with equivocal echocardiographic images or in cases of high clinical suspicion of LV thrombus.</i> | Ila | C |
| <i>Oral anticoagulant therapy (VKA or NOAC) should be considered for 3–6 months in patients with confirmed LV thrombus.</i> | Ila | C |
| <i>Following an acute anterior MI, a contrast echocardiogram may be considered for the detection of LV thrombus if the apex is not well visualized on echocardiography.</i> | Ilb | C |
| Atrial fibrillation: | | |
| <i>Intravenous beta-blockers are recommended when rate control is needed in the absence of acute HF or hypotension.</i> | I | C |
| <i>Intravenous amiodarone is recommended when rate control is needed in the presence of acute HF and no hypotension.</i> | I | C |
| <i>Immediate electrical cardioversion is recommended in patients with ACS and haemodynamic instability and when adequate rate control cannot be achieved promptly with pharmacological agents.</i> | I | C |
| <i>Intravenous amiodarone is recommended to facilitate electrical cardioversion and/or decrease risk for early recurrence of AF after electrical cardioversion in unstable patients with recent-onset AF.</i> | I | C |
| <i>In patients with documented de novo AF during the acute phase of ACS, long-term oral anticoagulation should be considered depending on the CHA₂DS₂-VASc score, after taking the HAS-BLED score and the need for concomitant antiplatelet therapy into consideration. NOACs are the preferred drugs.</i> | Ila | C |
| Ventricular arrhythmias: | | |

| | | |
|--|------------|----------|
| <i>ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic HF (NYHA Class II–III) and LVEF \leq 35% despite optimal medical therapy for > 3 months and at least 6 weeks after MI who are expected to survive for at least 1 year with good functional status.</i> | I | A |
| <i>Intravenous beta-blocker and/or amiodarone treatment is recommended for patients with polymorphic VT and/or VF unless contraindicated.</i> | I | B |
| <i>Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF.</i> | I | C |
| <i>Transvenous catheter pacing termination and/or overdrive pacing should be considered if VT cannot be controlled by repeated electrical cardioversion.</i> | IIa | C |
| <i>Radiofrequency catheter ablation at a specialized ablation centre followed by ICD implantation should be considered in patients with recurrent VT, VF, or electrical storm despite complete revascularization and optimal medical therapy.</i> | IIa | C |
| <i>Treatment of recurrent VT with haemodynamic relevance (despite repeated electrical cardioversion) with lidocaine may be considered if beta-blockers, amiodarone, and overdrive stimulation are not effective/applicable.</i> | IIb | C |
| <i>In patients with recurrent life-threatening ventricular arrhythmias, sedation or general anaesthesia to reduce sympathetic drive may be considered.</i> | IIb | C |
| <i>ICD implantation or the temporary use of a wearable cardioverter defibrillator may be considered <40 days after MI in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after STEMI onset, polymorphic VT or VF).</i> | IIb | C |
| <i>Treatment of asymptomatic and haemodynamically irrelevant ventricular arrhythmias with anti-arrhythmic drugs is not recommended.</i> | III | C |

| Bradyarrhythmias | | |
|---|-----|---|
| <p>In cases of sinus bradycardia with haemodynamic intolerance or high-degree AV block without stable escape rhythm:</p> <ul style="list-style-type: none"> - <i>i.v. positive chronotropic medication (adrenaline, vasopressin, and/or atropine) is recommended.</i> - <i>temporary pacing is recommended in cases of failure to respond to atropine.</i> - <i>urgent angiography with a view to revascularization is recommended if the patient has not received previous reperfusion therapy.</i> | I | C |
| <i>Implantation of a permanent pacemaker is recommended when high-degree AV block does not resolve within a waiting period of at least 5 days after MI.</i> | I | C |
| <i>In selected patients with high-degree AV block in the context of an anterior wall MI and acute HF, early device implantation (CRT-D/CRT-P) may be considered.</i> | IIb | C |
| <i>Pacing is not recommended if high-degree AV block resolves after revascularization or spontaneously.</i> | III | B |

Important trials in STEMI:

| Table 7-15: Clinical trials of STEMI: | |
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| Trial (date) | Summary |
| ACE inhibitors: | |
| ISIS-4 (1995) | <p>Aim: To assess if captopril, oral mononitrate and i.v magnesium will decrease short-term mortality when given routinely early after acute MI.</p> <p>Study: 58,050 patients after the onset of suspected AMI with no clear contraindications to the study treatments were randomised in a "2 x 2 x 2 factorial" study. The treatment comparisons were: (i) 1 month of oral captopril (6.25 mg initial dose titrated up to 50 mg twice daily) versus matching placebo; (ii) 1 month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg once daily) versus matching placebo; and (iii) 24 h of intravenous magnesium sulphate (8 mmol initial bolus followed by 72 mmol) versus open control. Captopril showed a reduction in mortality at 5 weeks with the largest advantage in high-risk individuals. There was no mortality benefit for isosorbide mononitrate or IV magnesium.</p> |
| GISSI-3 (1995) | <p>Aim: To assess the efficacy of lisinopril, transdermal GTN, and their combination in improving survival and ventricular function after acute MI.</p> <p>Study: 19,394 eligible patients presented within 24 h of symptom onset were randomly assigned 6 weeks of oral lisinopril (5 mg initial dose and then 10 mg daily) or open control as well as nitrates or open control. Lisinopril when given within 24 hours of acute MI reduced mortality by 11% at 6 weeks. No benefit for transdermal glyceryl trinitrate. This led to the use of ACE inhibitors for acute MI patients.</p> |
| Aldosterone antagonists: | |
| EPHESUS (2003) | <p>Aim: To determine the efficacy of eplerenone in patients with acute MI complicated by heart failure and systolic LV dysfunction.</p> |

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| | <p>Study: 6632 patients were randomly assigned to eplerenone (25 mg per day initially, titrated to a maximum of 50 mg per day) or placebo in addition to optimal medical therapy. The study continued until 1012 deaths occurred. The primary end points were all-cause mortality and CV mortality or hospitalization for HF, AMI, stroke, or ventricular arrhythmia. The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute MI complicated by LV dysfunction and heart failure.</p> |
| <p>REMINDER (2014)</p> | <p>Aim: To assess the impact of eplerenone on CV outcomes in STEMI without known heart failure, when initiated within 24 h of symptom onset.</p> <p>Study: 1012 patients with acute STEMI and without a history of heart failure were randomly assigned to receive either eplerenone (25–50 mg once daily) or placebo in addition to standard therapy. The primary endpoint was the composite of CV mortality, re-hospitalization, or, extended initial hospital stay, due to diagnosis of HF, sustained VT or VF, LVEF ≤ 40%, or elevated BNP/NT-proBNP at 1 month or more after randomization. Eplerenone reduced the primary endpoint over a mean 13 months follow-up mostly because of significantly lower BNP/NT-proBNP levels.</p> |
| <p>Thrombolysis:</p> | |
| <p>ISIS-2 (1988)</p> | <p>Aim: To assess whether the combination of Streptokinase and aspirin was better than either agent alone in preventing vascular death.</p> <p>Study: 17,187 patients after the onset of suspected acute MI were randomised, with placebo control, between: (i) a 1-hr i.v infusion of 1.5 MU of streptokinase; (ii) one month of 160 mg/day enteric-coated aspirin; (iii) both active treatments; or (iv) neither. The combination of aspirin and streptokinase was better than either agent alone. Aspirin reduced non-fatal reinfarction without increasing bleeding risk. Streptokinase alone increased bleeding requiring transfusion, intracranial hemorrhage and non-fatal re-infarction if used alone. Survival benefit of combination of aspirin and streptokinase extended out at least 10 years.</p> |
| <p>ISIS-3 (1992)</p> | <p>Aim: To determine the balance between the benefits and risks of different antithrombotic regimens and of different fibrinolytic regimens</p> |

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| | <p>Study: 41,299 patients after the onset of suspected AMI were randomised between streptokinase (SK: 1.5 MU infused over about 1 h), tissue plasminogen activator (0.60 MU/kg infused over about 4 h), or anisoylated plasminogen-streptokinase activator complex (APSAC), anistreplase: 30 U over about 3 min). Each thrombolytic agent was similar in primary endpoint of 35 day mortality. There was increased bleeding when heparin was used with the thrombolytic agent including intracranial hemorrhage with small reduction in death which ceased once heparin was stopped.</p> |
| Beta-blockers: | |
| ISIS-1 (1986) | <p>Aim: To assess the effects of early beta-blockade following acute MI.</p> <p>Study: 16,027 patients after the onset of suspected AMI were randomised either to atenolol (5-10 mg iv immediately, followed by 100 mg/day orally for 7 days) or placebo. Primary endpoint was vascular mortality. Beta blockade, administered early in the course of MI, improves clinical outcome.</p> |
| COMMIT (2005) | <p>Aim: To evaluate treatment with metoprolol compared with placebo among patients with STEMI also treated with aspirin.</p> <p>Study: 45,852 patients with suspected acute MI were randomly allocated metoprolol (up to 15 mg i.v then 200 mg oral daily) or matching placebo. Primary Endpoints were: (1) All-cause mortality by hospital discharge; and (2) all-cause mortality, nonfatal reinfarction, or ventricular fibrillation/arrest by hospital discharge. Metoprolol was not associated with a reduction in the primary endpoints of mortality or death, reinfarction, or cardiac arrest compared with placebo.</p> |
| Nitrates | |
| GISSI-3 (1995) | <p>GTN</p> <p>See before</p> |
| ISIS-4 (1995) | <p>oral mononitrate</p> <p>See before</p> |
| Dibetic control: | |
| DIGAMI-1 | <p>Aim: To assess the effect of rapid improvement of metabolic control in diabetic patients with insulin-glucose infusion on mortality and morbidity.</p> |

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| (1995) | <p>Study: 620 patients with DM and AMI were randomized to treatment with insulin-glucose infusion followed by multidose subcutaneous insulin for ≥ 3 months and to conventional therapy. Insulin-glucose infusion improved long-term prognosis in diabetic patients with AMI.</p> |
| DIGAMI-2 (2005) | <p>Aim: To compare three treatment strategies: group 1, acute insulin-glucose infusion followed by insulin-based long-term glucose control; group 2, insulin-glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice.</p> <p>Study: 1253 patients with type 2 diabetes and suspected AMI were randomly assigned to groups: (1) acute insulin-glucose infusion followed by insulin-based long-term glucose control, (2) insulin-glucose infusion followed by standard glucose control, and (3) routine metabolic management according to local practice. DIGAMI 2 did not support the fact that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following MI when compared with a conventional management at similar levels of glucose control or that insulin-based treatment lowers the number of non-fatal myocardial reinfarctions and strokes. However, an epidemiological analysis confirms that the glucose level is a strong, independent predictor of long-term mortality in this patient category, underlining that glucose control seems to be important part of management.</p> |
| Lipid Lowering therapy: | |
| PROVE-IT (2004) | <p>Aim: To evaluate the efficacy of aggressive lipid lowering using atorvastatin in ACS compared with standard lipid lowering with pravastatin.</p> <p>Study: 4162 patients who had been hospitalized for ACS within the preceding 10 days and compared pravastatin (40mg daily; standard therapy) with atorvastatin (80 mg daily; intensive therapy). The primary end point was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean follow-up was 24 months. Intensive lipid-lowering statin regimen provides greater protection against death or MACE than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL-C to levels substantially below current target levels.</p> |

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| IMPROV E-IT (2015) | <p>Aim: To evaluate the effect of ezetimibe combined with simvastatin, compared with simvastatin alone, in stable patients who had had an ACS and whose LDL-C values were within guideline recommendations.</p> <p>Study: 18,144 patients who had been hospitalized for ACS within the preceding 10 days and had LDL-C levels of (50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not receiving lipid-lowering therapy). The combination of simvastatin and ezetimibe was compared with simvastatin monotherapy. The median follow-up was 6 years. When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C and improved CV outcomes. Moreover, lowering LDL-C to levels below previous targets provided additional benefit.</p> |
| Anti-inflammatory drugs: | |
| COLCOT (2019) | <p>Aim: To evaluate the effects of colchicine on CV outcomes as well as its long-term safety profile in patients who had recently had a MI.</p> <p>Study: 4745 patients were randomly assigned within 30 days after MI to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization. Colchicine (0.5 mg daily) led to a significantly lower risk of ischemic cardiovascular events than placebo.</p> |
| COVERT MI (2021) | <p>Aim: To evaluate the effect of colchicine on the injury after acute MI assessed by cardiac MRI.</p> <p>Study: 192 patients admitted for a first episode of STEMI referred for primary PCI were randomly assigned to receive oral colchicine (2-mg loading dose followed by 0.5 mg twice a day) or matching placebo from admission to day 5. Oral administration of high-dose colchicine at the time of reperfusion and for 5 days did not reduce infarct size assessed by cardiac MRI.</p> |
| Oxygen therapy: | |
| DETO2X (2017) | <p>Aim: To evaluate supplemental oxygen therapy compared with ambient air among patients with suspected AMI.</p> <p>Study: 6629 patients with suspected MI and oxygen saturation of 90% or higher were randomly assigned to receive either supplemental oxygen (6 L/min for 6 to 12 hours, delivered through an open face mask) or ambient air. Routine</p> |

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| | <i>use of supplemental oxygen in patients with suspected MI who did not have hypoxemia was not found to reduce 1-year all-cause mortality.</i> |
| Blood transfusion: | |
| REALITY (2020) | <p>Aim: <i>To assess the safety and efficacy of a restrictive versus liberal RBC transfusion strategy in patients with acute MI and anemia.</i></p> <p>Study: <i>666 patients with AMI and Hb ≤ 8 to ≤ 10 g/dl during admission were randomized to either a liberal (for Hb ≤ 10 g/dl, goal Hb >11 g/dl) or a restrictive (for Hb ≤ 8 g/dl, target Hb 8-10 g/dl) RBC transfusion strategy. The strategies should be maintained until discharge from hospital or for 30 days, whichever comes first. Restrictive PRBC transfusion strategy (transfusion for Hgb ≤ 8 g/dl, goal 8-10 g/dl) is noninferior to a more liberal strategy (transfusion for Hb ≤ 10 g/dl, goal Hb > 11 g/dl) at 30 days. In addition, infections and acute lung injury were higher with a more liberal strategy.</i></p> |
| MINT (2023) | <p>Aim: <i>To assess the safety and efficacy of a restrictive versus liberal RBC transfusion strategy in patients with acute MI and anemia.</i></p> <p>Study: <i>3504 patients with MI and a Hb level of less than 10 g/dl were randomly assigned to a restrictive transfusion strategy (Hb cutoff for transfusion, 7 or 8 g per deciliter) or a liberal transfusion strategy (Hb cutoff, <10 g per deciliter). The primary outcome was a composite of MI or death at 30 days. A liberal transfusion strategy did not significantly reduce the risk of recurrent MI or death at 30 days. However, potential harms of a restrictive transfusion strategy cannot be excluded.</i></p> |
| Revascularization in STEMI: | |
| NORDISTE MI (2009) | <p>Aim: <i>To evaluate immediate transfer for PCI compared with conservative, ischemia-guided treatment among patients with STEMI treated with thrombolysis with very long transfer times to PCI hospitals.</i></p> <p>Study: <i>266 patients were treated with optimal medical therapy (tenecteplase, aspirin, enoxaparin, and clopidogrel) and were then randomized to immediate transfer for angiography/PCI or ischemia-guided treatment in local hospitals with transfer for rescue PCI if needed. SPECT was performed at 3 months of follow-up. Immediate transfer</i></p> |

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| | <i>for PCI did not improve the primary outcome, but reduced the rate of death, reinfarction, or stroke at 12 months in patients with STEMI, treated with thrombolysis and clopidogrel in areas with long transfer distances.</i> |
| COMFORT ABLE AMI (2012) | <p>Aim: <i>To evaluate treatment with a biolimus-eluting stent with biodegradable polymer compared with bare-metal stent in patients with STEMI.</i></p> <p>Study: <i>1,157 patients with STEMI were randomized to a Biomatrix biolimus-eluting stent with biodegradable polylactic acid polymer versus a bare-metal stent. Aspiration thrombectomy was recommended prior to stent implantation. The use of a novel biolimus-eluting stent with biodegradable polymer was superior to a bare-metal stent. This device reduced target vessel reinfarction and ischemia-driven target lesion revascularization.</i></p> |
| TAPAS (2008) | <p>Aim: <i>To evaluate a strategy of thrombus aspiration during primary PCI compared with conventional PCI in patients with STEMI.</i></p> <p>Study: <i>1071 patients undergoing primary PCI were randomly assigned to the thrombus-aspiration group or the conventional-PCI group before undergoing coronary angiography. Aspiration was considered to be successful if there was histopathological evidence of atherothrombotic material. Thrombus aspiration is applicable in a large majority of patients with STEMI, and it results in better reperfusion and clinical outcomes than conventional PCI, irrespective of clinical and angiographic characteristics at baseline.</i></p> |
| OAT (2006) | <p>Aim: <i>To assess whether routine PCI for total occlusion of the IRA 3 to 28 days after acute MI would reduce the occurrence of a composite end point of death, reinfarction, or NYHA IV heart failure.</i></p> <p>Study: <i>2166 stable patients who had total occlusion of the IRA 3 to 28 days after MI and who met a high-risk criterion (an ejection fraction of <50% or proximal occlusion) were randomly assigned to routine PCI with optimal medical therapy, <u>or</u> optimal medical therapy alone. The primary end point was a composite of death, myocardial reinfarction, or NYHA class IV HF. PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up.</i></p> |
| IRA-only PCI or complete revascularization: | |

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| CULPRIT-SHOCK (2017) | <p>Aim: To assess safety and efficacy of culprit-lesion-only PCI versus multivessel PCI among patients presenting with acute MI and cardiogenic shock in the setting of multivessel disease.</p> <p>Study: 706 patients who had multivessel disease, AMI, and cardiogenic shock were randomly assigned to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. The primary end point was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. The 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent immediate multivessel PCI.</p> |
| PRAMI (2013) | <p>Aim: To compare outcomes between PPCI of all significant lesions versus PPCI of the IRA in patients with STEMI who had multiple stenoses.</p> <p>Study: 465 patients with acute STEMI who were undergoing IRA PCI were randomly assigned them to either preventive PCI or no preventive PCI. Preventive PCI in noninfarct coronary arteries with major stenoses significantly reduced the risk of adverse cardiovascular events, as compared with PCI limited to the infarct artery.</p> |
| CvLPRIT (2015) | <p>Aim: To evaluate PCI of the IRA compared with complete revascularization at the index admission in patients with STEMI.</p> <p>Study: 296 patients who have multivessel disease while undergoing primary PCI for STEMI were randomized to either in-hospital complete revascularization or IRA-only revascularization. Complete revascularization was performed either at the time of P-PCI or before hospital discharge. The primary endpoints were mortality, MI, heart failure, and ischemia-driven revascularization at 12 months. Index admission complete revascularization significantly lowered the rate of the composite primary endpoint at 12 months compared with treating only the IRA.</p> |
| COMPLETE (2019) | <p>Aim: To compare complete revascularization with culprit-only revascularization in patients with STEMI and multivessel coronary disease.</p> <p>Study: 4,041 patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI were randomly assigned to a strategy of either complete revascularization with PCI of angiographically significant</p> |

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| | <i>nonculprit lesions or no further revascularization. Among patients with STEMI and multivessel coronary artery disease, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of CV death or MI, as well as the risk of CV death, MI, or ischemia-driven revascularization.</i> |
| DANAMI-3 PRIMUM TI (2015) | <p>Aim: <i>To compare the utility of IRA PCI versus FFR-guided complete revascularization in patients with STEMI and multivessel disease.</i></p> <p>Study: <i>627 patients presenting with STEMI who had one or more clinically significant coronary stenosis in addition to the lesion in the infarct-related artery were included. After successful PCI of the infarct-related artery, patients were randomly allocated either no further invasive treatment or complete FFR-guided revascularisation before discharge. Complete revascularisation guided by FFR measurements significantly reduces the risk of future events compared with no further invasive intervention after primary PCI. This effect is driven by significantly fewer repeat revascularisations, because all-cause mortality and non-fatal reinfarction did not differ between groups. Thus, to avoid repeat revascularisation, patients can safely have all their lesions treated during the index admission.</i></p> |
| COMPARE-ACUTE (2017) | <p>Aim: <i>To evaluate PCI of the IRA compared with FFR-guided complete revascularization at the index admission in patients with STEMI.</i></p> <p>Study: <i>885 patients with STEMI and multivessel disease who had undergone primary PCI of an IRA were randomly assigned in a 1:2 ratio to undergo complete revascularization of non-IRA guided by FFR or to undergo no revascularization of non-IRA. The primary end point was a composite of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months. The addition of FFR-guided complete revascularization of non-IRA in the acute setting resulted in a risk of a composite cardiovascular outcome that was lower than the risk among those who were treated for the IRA only. This finding was mainly supported by a reduction in subsequent revascularizations.</i></p> |
| MULTISTARS AMI (2023) | <p>Aim: <i>To investigate whether PCI for non-culprit lesions should be attempted during the index procedure or staged.</i></p> <p>Study: <i>840 Patients in a hemodynamically stable condition who had STEMI and multivessel coronary artery disease were randomly assigned to undergo immediate multivessel percutaneous coronary intervention (PCI; immediate</i></p> |

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| | <p>group) or PCI of the culprit lesion followed by staged multivessel PCI of nonculprit lesions within 19 to 45 days after the index procedure (staged group). The primary end point was a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year after randomization. Immediate multivessel PCI was noninferior to staged multivessel PCI with respect to the risk of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year.</p> |
| BIOVASC (2023) | <p>Aim: To investigate whether PCI for non-culprit lesions should be attempted during the index procedure or staged.</p> <p>Study: 764 patients with STEMI or NSTEMI-ACS and multivessel coronary artery disease with a clearly identifiable culprit lesion. A were randomly assigned to undergo immediate complete revascularisation or staged complete revascularisation (PCI of only the culprit lesion during the index procedure and PCI of all non-culprit lesions within 6 weeks after the index procedure). The primary outcome was the composite of all-cause mortality, MI, any unplanned ischaemia-driven revascularisation, or cerebrovascular events at 1 year after the index procedure. In patients presenting with ACS and multivessel disease, immediate complete revascularisation was non-inferior to staged complete revascularisation for the primary composite outcome and was associated with a reduction in MI and unplanned ischaemia-driven revascularisation.</p> |

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Chapter 8:

Non-ST-Elevation Acute Coronary Syndrome

Definition:

Unstable angina: is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. It is characterized by any of the following clinical presentations, with or without ECG evidence of ischemia and with a normal troponin:

- Crescendo angina: angina that increases in frequency, intensity, or duration, often requiring a more frequent use of nitroglycerin.
- New-onset (< 2 months) severe angina, occurring during normal activities performed at a normal pace.
- Rest angina.
- Angina occurring within 2 weeks after a myocardial infarction (post-infarction angina).

NSTEMI is defined as MI without persistent (> 20 min) ST-segment elevation ⁽¹⁾.

MI is defined as a troponin elevation above the 99th percentile of the reference limit with a rise and/or fall pattern ⁽²⁾, along with any one of the following four features:

1. Angina.
2. ST-T abnormalities, new LBBB, or new Q waves on ECG.
3. New wall motion abnormality on imaging.
4. Intracoronary thrombus on angiography.

(1) For practical purposes, ischemic symptoms with ongoing ST-elevation of any duration are considered and managed as STEMI. The diagnosis may be retrospectively changed to NSTEMI if ST elevation resolves without reperfusion therapy, in < 20 minutes.

(2) A rise or fall in troponin is necessary to define MI. A mild, chronically elevated but stable troponin may be seen in chronic heart failure, severe LVH, or advanced kidney disease. While having a prognostic value, this stable troponin rise is not diagnostic of MI.

Unstable angina and NSTEMI are grouped together as NSTEMI-ACS. However, unstable angina has a much better prognosis than NSTEMI, particularly that many patients labeled as unstable angina do not actually have true angina, and if they do, the underlying CAD is stable CAD, sometimes severe, but not ACS. In fact, in the current era of highly sensitive troponin assays, a true ACS with coronary thrombosis or resting pain is accompanied by a troponin rise. Unstable angina is, thus, a vanishing entity.

Pathophysiology:

The pathogenesis of NSTEMI-ACS involves four processes operating singly or in various combinations:

- **Disruption of an unstable atheromatous plaque**, which may be driven at least in part by inflammation.
Three forms of disruptions of coronary artery plaques can precipitate thrombosis: plaque rupture (most common), plaque erosion, and disruptive nodular calcification protruding into the lumen.
Activation of the coagulation cascade and platelets plays central roles in the formation of thrombus following plaque disruption.
- **Activation of the platelets**: The first step in thrombus formation is vascular injury that causes adhesion of *platelets to the arterial wall* via binding of platelet glycoprotein Ib to subendothelial von Willebrand factor. Exposure of platelets to subendothelial collagen and/or circulating thrombin causes platelet activation, which induces platelets to change shape and results in their degranulation with release of ADP and thromboxane A₂, which cause further platelet activation and expression of platelet GP IIb/IIIa.
- **Activation of the coagulation cascade**: tissue factor expressed within the lipid-rich core of atherosclerotic plaque, when exposed to circulating blood, activates the coagulation cascade.
A complex of tissue factor and coagulation factors VIIa and Va leads to the formation of activated factor X (factor Xa), which in turn amplifies the production of activated factor IIa (thrombin). This cascade proceeds with thrombin-induced conversion of fibrinogen to fibrin.
- Platelet GP IIb/IIIa binds circulating fibrinogen, thereby causing platelet aggregation and ultimately producing **a platelet-fibrin thrombus, portions of it may embolize distally and cause myocardial necrosis.**

| Table 8-1: Main Characteristics of Plaque Rupture and Superficial Erosion: | |
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| Plaque Rupture | Plaque Erosion |
| <i>Lipid rich</i> | <i>Lipid poor</i> |
| <i>Collagen poor, thin fibrous cap</i> | <i>Proteoglycan and glycosaminoglycan rich</i> |
| <i>Interstitial collagen breakdown</i> | <i>Nonfibrillar collagen breakdown</i> |
| <i>Abundant inflammation</i> | <i>Few inflammatory cells</i> |
| <i>Smooth muscle cell apoptosis</i> | <i>Endothelial cell apoptosis</i> |
| <i>Macrophage predominance</i> | <i>Secondary neutrophil involvement</i> |
| <i>Male predominance</i> | <i>Female predominance</i> |
| <i>High level of LDL cholesterol</i> | <i>High level of triglycerides</i> |

- **Secondary unstable angina and NSTEMI:** In this case, ischemia is related to severely increased O₂ demands (demand/supply mismatch). The patient may have underlying CAD but the coronary plaques are stable without acute rupture or thrombosis. Conversely, the patient may not have any underlying CAD. *Acute antithrombotic therapy is not warranted.*
 - Cardiac causes of secondary NSTEMI-ACS include: severe hypertension, acute HF, tachyarrhythmias.
 - Non-cardiac causes of secondary NSTEMI-ACS include: GI bleed, severe anemia, hypoxia, sepsis.
- **Coronary arterial vasoconstriction:** Vasoconstriction causing dynamic obstruction of coronary arterial flow may result from spasm of the epicardial coronary arteries (Prinzmetal angina) **or** from constriction of small, intramural muscular coronary arteries.
- **Gradual intraluminal narrowing of an epicardial coronary artery** caused by progressive atherosclerosis or restenosis after stenting.

Diagnosis:

- **Clinical presentation and ECG:**

- Acute chest discomfort is characterized by a retrosternal sensation of pain, pressure, or heaviness (angina) radiating to the left arm (less frequently to both arms or to the right arm), the neck, or the jaw, which may be intermittent or persistent. Chest pain descriptors should be classified as cardiac, possibly cardiac, and likely non-cardiac. The use of the descriptor 'atypical' should be avoided.
- It is recommended to obtain an ECG within 10 min of first medical contact. Based on the ECG, two groups of patients should be differentiated:
 - Patients with acute chest pain and persistent (> 20 min) ST-elevation. This is termed (STEMI).
 - Patients with acute chest discomfort but no persistent ST-segment elevation (NSTEMI) exhibit ECG changes that may include transient ST-segment elevation, persistent or transient ST-depression, inverted or flat T, or pseudonormalization of T waves; or the ECG may be normal ⁽¹⁾.
- Among unselected patients presenting with acute chest pain to the emergency department, disease prevalence can be expected to be the following: 5-10% STEMI, 15-20% NSTEMI, 10% unstable angina, 15% other cardiac conditions, and 50% non-cardiac diseases. Several cardiac and non-cardiac conditions may mimic NSTEMI. Conditions that should always be considered in the differential diagnosis of NSTEMI because they are potentially life-threatening but also treatable include: aortic dissection, pulmonary embolism, and tension pneumothorax. Echocardiography should be performed urgently in all patients with haemodynamic instability of suspected cardiovascular origin.
- **Biomarkers:**
 - Measurement of a biomarker of cardiomyocyte injury, preferably hs-cTn is mandatory in all patients with suspected NSTEMI. Compared with standard cardiac troponin assays, hs-cTn assays:
 - Have higher NPV for AMI.
 - Reduce the 'troponin-blind' interval leading to earlier detection of AMI.

(1) Only 50% of patients with NSTEMI have an ischemic ECG, and 20% of NSTEMIs have an absolutely normal ECG. Yet, patients with ischemic ECG are higher-risk patients and most often have LAD or multivessel involvement.

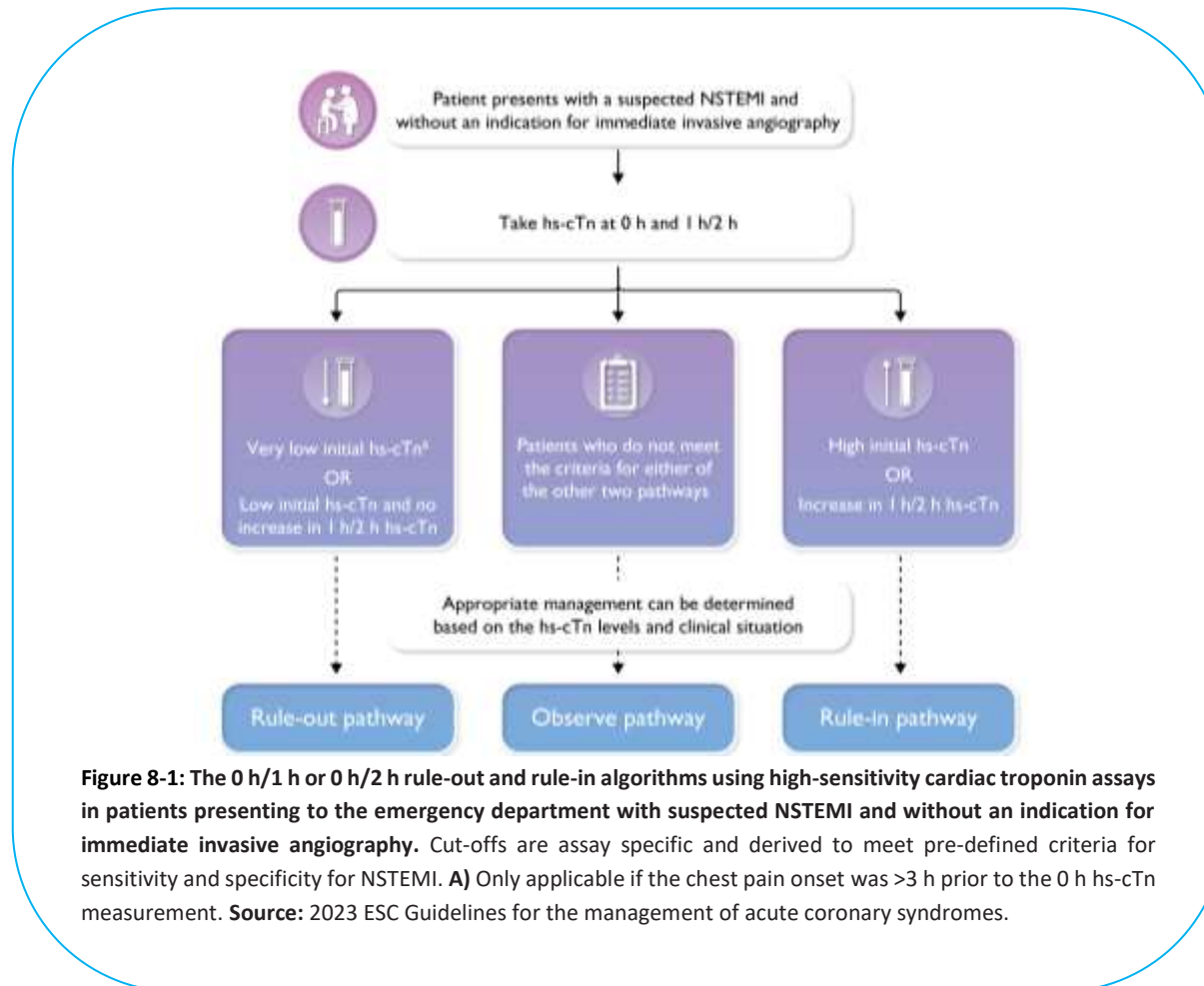
- Result in 4% absolute and 20% relative increases in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
- Are associated with a 2-fold increase in the detection of type 2 MI.
- Levels of hs-cTn should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
 - Elevations beyond 5-fold the upper reference limit have high (> 90%) PPV for acute type 1 MI.
 - Elevations up to 3-fold the upper reference limit have only limited (50-60%) PPV for AMI.
 - It is common to detect circulating levels of cardiac troponin in healthy individuals.
- Rising and/or falling troponin levels differentiate acute (as in MI) from chronic cardiomyocyte damage.
- In patients presenting with suspected NSTEMI-ACS, four clinical variables affect hs-cTn concentrations beyond the presence or absence of MI. These variables are: **(1)** Age (concentrations in healthy very young vs. 'healthy' very old individuals differ by up to 300%); **(2)** Renal dysfunction (differences between otherwise healthy patients with very high vs. very low eGFR of up to 300%); **(3)** Time from chest pain onset (> 300%); and, to a lesser extent, **(4)** Sex (≈ 40%).
- **Rapid 'rule-in' and 'rule-out' algorithms:**

Due to the higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of hs-cTn assays. It is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second best option, blood draw at 0 h and 2 h).

Patients are classified into one of three pathways as per the results of their hs-cTn values at 0 h (time of initial blood test) and 1 h or 2 h later:

 - (1)** Patients with a very low initial hs-cTn value or patients with a low initial value and no 1 h/2 h change in hs-cTn are assigned to the '**rule-out**' pathway (NPV for MI > 99%). Even after the ruling out of MI, elective non-invasive or invasive imaging may be appropriate according to clinical and risk assessment, and an alternative diagnosis to MI should be identified.
 - (2)** Patients with high initial hs-cTn **or** a 1 h/2 h change in hs-cTn are assigned to the '**rule-in**' pathway (PPV for MI is ~70-75%). Those patients will require admission and invasive coronary angiography.

(3) Patients who do not meet the criteria for the rule-out or rule-in strategies are assigned to the '**observe**' pathway. These patients should have hs-cTn levels checked at 3 h ± echocardiography in order to decide on further management. Most patients in the observe zone with a high degree of clinical suspicion of ACS are candidates for ICA. Conversely, most patients with a low to intermediate likelihood for ACS according to clinical judgment are candidates for non-invasive imaging (e.g., CT angiography) after transfer from the ED to the ward.



▪ **Non-invasive imaging:**

○ **Functional evaluation:**

- **TTE** should be routinely available in emergency rooms and chest pain units. TTE is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis (i.e. segmental hypokinesia or akinesia). TTE can also help in detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy, mitral valve prolapse, or RV dilatation suggestive of acute pulmonary embolism. TTE is the diagnostic tool of choice for patients with haemodynamic instability of suspected cardiac origin.
- **Stress echocardiography** has demonstrated superior prognostic value over exercise ECG.
- If the acoustic window is not adequate to assess regional wall motion abnormalities, the use of **echocardiographic contrast** is recommended.
- **CMR** can assess both perfusion and wall motion abnormalities, and patients presenting with acute chest pain with a normal stress CMR have an excellent short- and mid-term prognosis.
- **SPECT** is useful for the risk stratification of patients with acute chest pain suggestive of ACS.

○ **Anatomical evaluation:**

- CCTA allows visualization of the coronary arteries, and a normal scan excludes CAD.
- CCTA is less useful in patients with known CAD and patients with previous PCI or CABG in acute settings.
- CCTA can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism and aortic dissection.

Table 8-2: ESC Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected NSTEMI-ACS:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| Diagnosis and risk stratification: | | |

| | | |
|---|------------|----------|
| <i>It is recommended to base diagnosis and initial short-term risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results including hs-cTn.</i> | I | B |
| <i>It is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling.</i> | I | B |
| <i>It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician.</i> | I | B |
| <i>It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.</i> | I | C |
| <i>The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.</i> | I | B |
| <i>Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.</i> | I | B |
| <i>As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs cTn test with a validated 0 h/2 h algorithm is available.</i> | I | B |
| <i>Additional ECG leads (V3R, V4R, V7-V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive.</i> | I | C |
| <i>As an alternative to the ESC 0 h/1 h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered, if a high-sensitivity (or sensitive) cardiac troponin test with a validated 0 h/3 h algorithm is available.</i> | Ila | B |
| <i>It should be considered to use established risk scores for prognosis estimation.</i> | Ila | C |

| | | |
|---|------------|----------|
| <i>For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as heart-type fatty acid binding protein (h-FABP) or copeptin, in addition to hs-cTn.</i> | III | B |
| Imaging: | | |
| <i>In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG.</i> | I | C |
| <i>In patients with suspected ACS, non-elevated (or uncertain) hs-cTn, no ECG changes and no recurrence of pain, incorporating CCTA or a non-invasive stress imaging test as part of the initial workup should be considered.</i> | Ila | A |
| <i>Emergency TTE should be considered at triage in cases of diagnostic uncertainty, but this should not result in delays in transfer to the cardiac catheterization laboratory if there is suspicion of an acute coronary artery occlusion.</i> | Ila | C |
| <i>CCTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.</i> | I | A |
| <i>Routine, early CCTA in patients with suspected ACS is not recommended ⁽¹⁾.</i> | III | B |
| Monitoring: | | |
| <i>Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI has been established or ruled out.</i> | I | C |
| <i>It is recommended to admit NSTEMI patients to a monitored unit.</i> | I | C |

(1) The BEACON study showed no reduction of in-hospital duration of stay or hospital admission in the CCTA arm compared with patients investigated with hs-cTn, with similar results to those observed in the ROMICAT II and RAPID-CTCA trials. In the latter study, a default approach using early non-invasive CCTA in patients with suspected NSTEMI-ACS did not improve clinical outcomes at 1 year and was associated with a modest increase in the duration and cost of the hospital stay.

| | | |
|--|------------|----------|
| <i>Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias ⁽¹⁾.</i> | I | C |
| <i>Rhythm monitoring for > 24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias ⁽²⁾.</i> | I | C |
| <i>In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in unstable angina may be considered in selected patients (e.g., suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events).</i> | IIb | C |

Risk assessment and outcomes:

• Clinical risk assessment:

GRACE risk score offers the best discriminative performance to estimate the future risk of all-cause mortality or the combined risk of all-cause mortality or MI. A GRACE risk score-based risk assessment has been found to be superior to (subjective) physician assessment for the occurrence of death or MI.

• Biomarkers for risk assessment:

- Beyond diagnostic utility, initial cardiac troponin levels add prognostic information in terms of short- and long-term mortality to clinical and ECG variables. *While hs-cTn T and I have comparable diagnostic accuracy, hs-cTn T has greater prognostic accuracy.*
- Natriuretic peptides (BNP/NT-proBNP) provide prognostic information on top of cardiac troponin regarding the risk of death, acute heart failure, as well as the development of AF.

○ Imaging risk assessment:

(1) *If none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF < 40%, failed reperfusion, additional critical coronary stenoses of major vessels, complications related to PCI, or GRACE risk score > 140 if assessed.*

(2) *If one or more of the above criteria are present.*

- LV dysfunction is a key prognostic factor for patients with ACS. It is recommended that the LVEF is determined before hospital discharge in all patients with ACS.
- In patients with a pre-discharge LVEF of $\leq 40\%$, re-evaluation of the LVEF 6–12 weeks after complete revascularization and optimal medical therapy is recommended to assess the potential need for primary prevention ICD implantation.

• **Bleeding risk assessment:**

Major bleeding events are associated with increased mortality in NSTEMI-ACS. The use of the CRUSADE bleeding risk score may be considered in patients undergoing coronary angiography to quantify bleeding risk. An alternative to these scores may be the assessment of bleeding risk according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR).

| Table 8-3: Major and minor criteria for high bleeding risk according to the Academic Research Consortium: | |
|---|--|
| Bleeding risk is high if at least one major <u>or</u> two minor criteria are met: | |
| Major | Minor |
| <ul style="list-style-type: none"> - Chronic bleeding diathesis - Liver cirrhosis with portal hypertension - Severe or end-stage CKD (eGFR < 30 mL/min) - Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent - Presence of a brain arteriovenous malformation - Previous spontaneous intracranial haemorrhage - Previous traumatic intracranial haemorrhage within the past 12 months - Moderate or severe ischaemic stroke (NIHSS score > 5) within the past 6 months | <ul style="list-style-type: none"> - Age ≥ 75 years - Moderate CKD (eGFR 30-59 mL/min) - Hb 11-12.9 g/dL for men or 11-11.9 g/dL for women - Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion. - Chronic use of oral NSAIDs or steroids - Any ischaemic stroke at any time not meeting the major criterion. |

| | |
|--|--|
| <ul style="list-style-type: none"> - Major surgery or major trauma within 30 days prior to PCI - Active malignancy ⁽¹⁾ (excluding non-melanoma skin cancer) within the past 12 months. - Haemoglobin < 11 g/dL - Baseline thrombocytopenia (plt before PCI < 100 x 10⁹/L) - Anticipated use of long-term OAC ⁽²⁾ - Non-deferrable major surgery on DAPT | |
|--|--|

| Table 8-4: ESC Recommendations on prognostic stratification in NSTEMI-ACS: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Biomarker measurements for prognostic stratification: | | |
| Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis. | I | B |
| Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information. | IIa | B |
| The measurement of additional biomarkers, such as mid-regional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, mid-regional pro adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment. | III | B |
| Score to risk stratify: | | |

(1) Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy)

(2) This excludes vascular protection doses.

| | | |
|--|------------|----------|
| <i>GRACE risk score models should be considered for estimating prognosis.</i> | Ila | B |
| <i>The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.</i> | IIb | A |
| <i>To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.</i> | IIb | B |

Pharmacological treatments:

▪ **Antithrombotic treatment:**

• **Antiplatelet drugs and pre-treatment:**

- DAPT including aspirin and a potent P2Y₁₂ receptor inhibitor (ticagrelor or prasugrel) is the recommended standard treatment for NSTEMI-ACS patients.
- Clopidogrel, characterized by less potent and variable platelet inhibition, should only be used when prasugrel or ticagrelor are contraindicated, not available, or cannot be tolerated due to an unacceptable high bleeding risk (HBR).
- Pre-treatment defines a strategy according to which antiplatelet drugs, usually a P2Y₁₂ receptor inhibitor, are given before coronary angiography and when the coronary anatomy is unknown to achieve sufficient platelet inhibition at the time of PCI. It is not recommended to administer routine pre-treatment with a P2Y₁₂ receptor inhibitor in NSTEMI-ACS patients in whom coronary anatomy is not known and an early invasive management is planned (lack of evidence).

• **Peri-interventional anticoagulant treatment:**

- Upon admission with NSTEMI-ACS, anticoagulation with any one of these four drugs should be initiated: **(i)** unfractionated heparin (UFH), **(ii)** enoxaparin, **(iii)** bivalirudin, and **(iv)** fondaparinux. During PCI, either UFH or bivalirudin is used.
- The dose of UFH used in NSTEMI is lower than the dose used in PE, with a PTT goal of 46-70 seconds.
- Anticoagulants are typically stopped after the performance of PCI. If PCI is not performed, anticoagulants are typically administered for at least 48 hours (up to 8 days). Longer therapy reduces rebound ischemia, which mainly occurs with heparin.

- Avoid switch between enoxaparin and UFH due to increased bleeding risk. If Enoxaparin is administered before PCI:
 - If patient received 1 mg/kg SQ within 8h of PCI and has already received two doses of enoxaparin, no additional anticoagulation is needed during PCI.
 - If enoxaparin was used 8-12 h ago or only one SQ dose was given, add 0.3 mg/kg IV during PCI.
 - If enoxaparin was used > 12h ago, give 0.5-0.75 mg/kg IV bolus.

| Table 8-5: ESC Recommendations for antithrombotic therapy in NSTEMI-ACS patients without AF undergoing PCI: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Antiplatelet treatment: | | |
| <i>Aspirin is recommended for all patients without contraindications at an initial oral LD of 150-300 mg (or 75-250 mg i.v.), and at a MD of 75-100 mg o.d. for long-term treatment.</i> | I | A |
| <i>A P2Y12 receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding.</i> | I | A |
| Options are: <ul style="list-style-type: none"> - Prasugrel in P2Y12 receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥ 75 years or with a body weight < 60 kg). - Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.). - Clopidogrel (300-600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated. | I | B |
| | I | B |
| | I | C |
| <i>Prasugrel should be considered in preference to ticagrelor for NSTEMI-ACS patients who proceed to PCI.</i> | IIa | B |
| <i>GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no reflow or a thrombotic complication.</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>Cangrelor may be considered in P2Y12 receptor inhibitor- naïve patients undergoing PCI.</i> | IIb | A |
| <i>Pre-treatment with a P2Y12 receptor inhibitor may be considered in patients with NSTEMI-ACS who are not planned to undergo an early invasive strategy and do not have an HBR.</i> | IIb | C |
| <i>Treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.</i> | III | A |
| <i>It is not recommended to administer routine pre-treatment with a P2Y12 receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned.</i> | III | A |
| Peri-interventional anticoagulant treatment: | | |
| <i>Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment, at the time of diagnosis and, especially, during revascularization procedures according to both ischaemic and bleeding risks.</i> | I | A |
| <i>UFH (weight-adjusted i.v. bolus during PCI of 70-100 IU/kg, or 50-70 IU/kg in combination with a GP IIb/IIIa inhibitor; activated clotting time target range of 250-350 s, or 200-250 s if a GP IIb/IIIa inhibitor is given) is recommended in patients undergoing PCI.</i> | I | A |
| <i>In cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame, fondaparinux is recommended and, in such cases, a single bolus of UFH is recommended at the time of PCI.</i> | I | B |
| <i>It is recommended to select anticoagulation according to both ischaemic and bleeding risks, and according to the efficacy safety profile of the chosen agent.</i> | I | C |
| <i>Enoxaparin (i.v.) should be considered in patients pre-treated with subcutaneous enoxaparin.</i> | IIa | B |
| <i>Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.</i> | IIa | C |
| <i>Bivalirudin may be considered as an alternative to UFH.</i> | IIb | A |
| <i>Crossover of UFH and LMWH is not recommended.</i> | III | B |

- Post-interventional and maintenance treatment:

Table 8-6: ESC Recommendations for post-interventional and maintenance treatment in patients with NSTEMI-ACS:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with NSTEMI-ACS treated with coronary stent implantation, DAPT with a P2Y12 receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding.</i> | I | A |
| Prolonging antithrombotic treatment duration: | | |
| <i>Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without increased risk of major or life-threatening bleeding.</i> | IIa | A |
| <i>Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischaemic events and without increased risk of major or life-threatening bleeding.</i> | IIb | A |
| <i>In ACS patients with no prior stroke/transient ischaemic attack who are at high ischaemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.</i> | IIb | B |
| Shortening antithrombotic treatment duration: | | |
| <i>After stent implantation with high risk of bleeding (e.g. PRECISE-DAPT ≥ 25 or ARC HBR criteria met), discontinuation of P2Y12 receptor inhibitor therapy after 3 months should be considered.</i> | IIa | B |

| | | |
|---|------------|----------|
| <i>In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, SAPT (preferably with a P2Y12 receptor inhibitor) should be considered.</i> | IIa | A |
| <i>De-escalation of P2Y12 receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays.</i> | IIb | A |

○ **Risk criteria for extended treatment with a second antithrombotic agent:**

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy.

| Table 8-7: Risk criteria for extended treatment with a second antithrombotic agent: | |
|---|---|
| High thrombotic risk (Class IIa) | Moderate thrombotic risk (Class IIb) |
| <i>Complex CAD and at least 1 criterion</i> | <i>Non-complex CAD and at least 1 criterion</i> |
| Risk enhancers: | |
| <i>Diabetes mellitus requiring medication</i> <i>History of recurrent MI</i> <i>Polyvascular disease (CAD plus PAD)</i> <i>CKD with eGFR 15-59 mL/min/1.73 m²</i> | |

| | |
|--|--|
| <ul style="list-style-type: none"> ○ Premature (< 45 years) or accelerated (new lesion within a 2-year time frame) CAD. ○ Concomitant systemic inflammatory disease (e.g. HIV, SLE, chronic arthritis) ○ Any multivessel CAD | |
| Technical aspects: | |
| <ul style="list-style-type: none"> ○ At least 3 stents implanted. ○ At least 3 lesions treated. ○ Total stent length > 60 mm ○ History of complex revascularization (left main, bifurcation stenting with ≥ 2 stents implanted, CTO, stenting of last patent vessel) ○ History of stent thrombosis on antiplatelet treatment | |

▪ **Pharmacological treatment of ischaemia:**

| Table 8-8: ESC Recommendations for anti-ischemic drugs in the acute phase of NSTEMI-ACS: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Sublingual or i.v. nitrates and early initiation of beta-blocker treatment are recommended in patients with ongoing ischaemic symptoms and without contraindications.</i> | I | C |
| <i>i.v. nitrates are recommended in patients with uncontrolled hypertension or signs of heart failure.</i> | I | C |
| <i>It is recommended to continue chronic beta blocker therapy unless the patient is in overt heart failure.</i> | I | C |

In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered, and beta-blockers avoided.

Ila

B

Invasive treatments:

An initial or early invasive strategy does not equate with early PCI. It rather equates with early coronary angiography for risk stratification and subsequent management by PCI, CABG, or medical therapy according to the angiographic findings. It is an early intent to revascularize. However, invasive coronary angiography carries a certain risk for procedure related complications, which has to be considered in management decisions.

Timing of invasive strategy: Three major trials (FRISC II, TACTICS-TIMI 18, RITA 3) established the benefit of an initial invasive strategy and showed that in high risk ACS patients ⁽¹⁾ this strategy reduces the combined endpoint of death and MI in comparison to an initial conservative strategy, particularly in patients with positive troponin, ST-segment changes, or TIMI risk score ≥ 3 (50% reduction in death/MI in those subgroups in all three trials, with an absolute risk reduction of ~5% at 30 days and 1 year). Those beneficial results were seen despite the narrow difference in revascularization rates between the initial invasive and initial conservative strategy. These trials did not address revascularization vs. no revascularization in high-risk ACS patients who angiographically qualify for revascularization, in which case revascularization is expected to show more striking benefits. These trials rather addressed the early intent to revascularize vs. the early intent to not revascularize.

Patients presenting with NSTEMI-ACS and MVD:

○ Management of multivessel disease in ACS complicated by cardiogenic shock:

Cardiogenic shock may occur in 4-11% of ACS patients. Nearly 80% of ACS patients with CS have MVD.

(1) Large scale application of urgent coronary angiography (< 2 h) in all comers with NSTEMI did not improve death or MI (ABOARD and EARLY trials).

Immediate coronary angiography, and PCI if feasible, is recommended. PCI during the index procedure should be restricted to the IRA only (CULPRIT-SHOCK trial) ⁽¹⁾.

In patients with coronary anatomy unsuitable for PCI, emergency CABG is recommended (Better 6-month survival; SHOCK trial).

- **Timing of non-IRA revascularization in ACS:**

Meta-analyses of non-randomized studies suggest that complete revascularization is associated with fewer deaths and MACE during follow-up in comparison to IRA-only PCI.

- **Evaluation of non-IRA stenosis severity (angiography vs. physiology):**

Microvascular constriction may also occur in the non-IRAs, leading to overestimation of the severity of non-IRA lesions during the PPCI procedure. Therefore, Functional invasive evaluation of non-IRA severity during the index procedure may be considered.

(1) *In the CULPRIT-SHOCK trial, IRA-only PCI was associated with a significant reduction in all-cause death or renal replacement therapy at 30-day follow-up. At 1-year follow-up, mortality did not differ significantly between the two groups.*

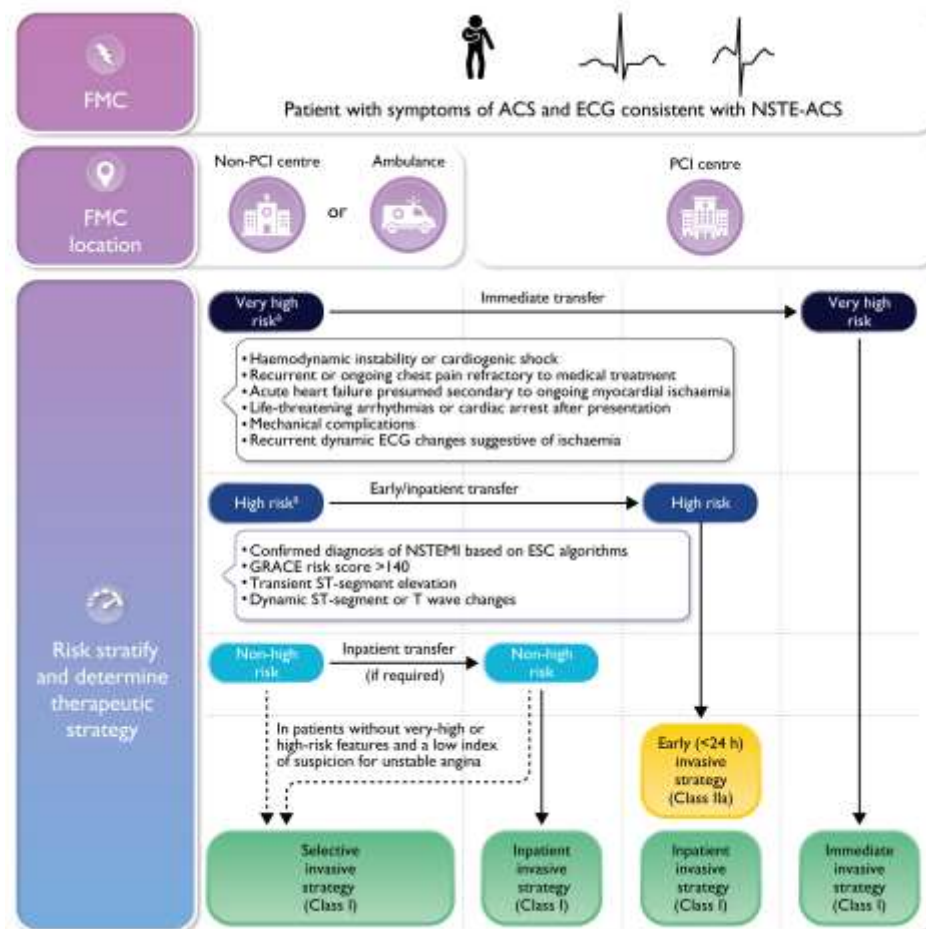


Figure 8-2: Selection of invasive strategy and reperfusion therapy in patients presenting with NSTEMI-ACS. This figure summarizes the selection of invasive strategy and reperfusion therapy in patients presenting with ACS. **Source:** 2023 ESC Guidelines for the management of acute coronary syndromes.

Table 8-9: ESC Recommendations for coronary revascularization in NSTEMI-ACS:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Timing to invasive strategy: | | |
| <i>An invasive strategy during hospital admission is recommended in NSTEMI-ACS patients with high-risk criteria or a high index of suspicion for unstable angina.</i> | I | A |
| <i>An immediate invasive strategy (< 2 h) is recommended in patients with at least one of the following very high-risk criteria:</i> <ul style="list-style-type: none"> ○ <i>Haemodynamic instability or cardiogenic shock.</i> ○ <i>Recurrent or refractory chest pain despite medical treatment.</i> ○ <i>Life-threatening arrhythmias or cardiac arrest after presentation.</i> ○ <i>Mechanical complications of MI.</i> ○ <i>Acute heart failure presumed secondary to ongoing myocardial ischaemia.</i> ○ <i>Recurrent dynamic ECG changes suggestive of ischaemia (particularly with intermittent ST-segment elevation).</i> | I | C |
| <i>An early invasive strategy within 24 h should be considered in patients with any of the following high-risk criteria:</i> <ul style="list-style-type: none"> ○ <i>Confirmed diagnosis of NSTEMI based on current recommended ESC hs-cTn algorithms.</i> ○ <i>Dynamic ST/T-segment changes suggesting ongoing ischaemia.</i> ○ <i>Transient ST-segment elevation.</i> ○ <i>GRACE risk score > 140.</i> | IIa | A |
| <i>A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk ⁽¹⁾.</i> | I | A |
| <i>Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents).</i> | III | A |

(1) These patients should be managed according to the Guidelines for the management of CCS. A selective invasive approach is also appropriate for patients with NSTEMI or UA who are not deemed good candidates for coronary angiography.

| | | |
|--|------------|----------|
| Technical aspects: | | |
| <i>Radial access is recommended as the standard approach, unless there are overriding procedural considerations.</i> | I | A |
| <i>DES are recommended over bare-metal stents for any PCI irrespective of clinical presentation, lesion type, planned non-cardiac surgery, anticipated duration of DAPT and concomitant anticoagulant therapy.</i> | I | A |
| <i>It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for stable CAD. However, the decision on immediate PCI of the culprit stenosis does not require Heart Team consultation.</i> | I | B |
| <i>Intracoronary imaging should be considered to diagnose SCAD if suspected.</i> | IIa | C |
| <i>FFR-guided revascularization of non-culprit NSTEMI-ACS lesion may be used during index PCI ⁽¹⁾.</i> | IIb | B |
| Multivessel disease with cardiogenic shock: | | |
| <i>IRA-only PCI during the index procedure is recommended.</i> | I | B |
| <i>Staged PCI of non-IRA should be considered (based on ischaemia, symptoms, patient comorbidities, and clinical condition.)</i> | IIa | C |
| Multivessel disease without cardiogenic shock: | | |
| <i>Complete revascularization should be considered in NSTEMI-ACS patients without CS and with multivessel CAD.</i> | IIa | C |
| <i>Complete revascularization during index PCI may be considered in NSTEMI-ACS patients with multivessel disease ⁽²⁾.</i> | IIb | B |

- (1)** Intracoronary imaging with IVUS or OCT is also useful to assess moderate NSTEMI lesions. In fact, in NSTEMI, the question is not only whether the lesion is functionally significant but whether the lesion is anatomically significant and likely to acutely progress (e.g., plaque rupture, thrombus). The goal of therapy in NSTEMI is to reduce the high risk of recurrent infarction rather than just improve angina; hence, the assessment of anatomy is more valuable in NSTEMI than in stable CAD. A thrombotic lesion that is not functionally significant at one point in time may still progress within days or weeks.
- (2)** When multiple complex lesions are seen in NSTEMI, the culprit artery may not be clearly identified and multivessel intervention is justified. The SMILE trial randomized NSTEMI patients with multivessel disease to multivessel PCI in one stage vs. multiple stages (2nd procedure 3-7 days later). Despite a similarly complete revascularization with only a few days difference, single-stage PCI was associated with significantly less repeat revascularizations at 1 year and a strong trend

Functional invasive evaluation of non-IRA severity during the index procedure may be considered.

IIb

B

toward less deaths. Somewhat similarly, in STEMI, multivessel PCI is to be performed; yet it does not have to be performed in the same setting and may await few days or weeks (COMPLETE, DANAMI- PRIMULTI trials).

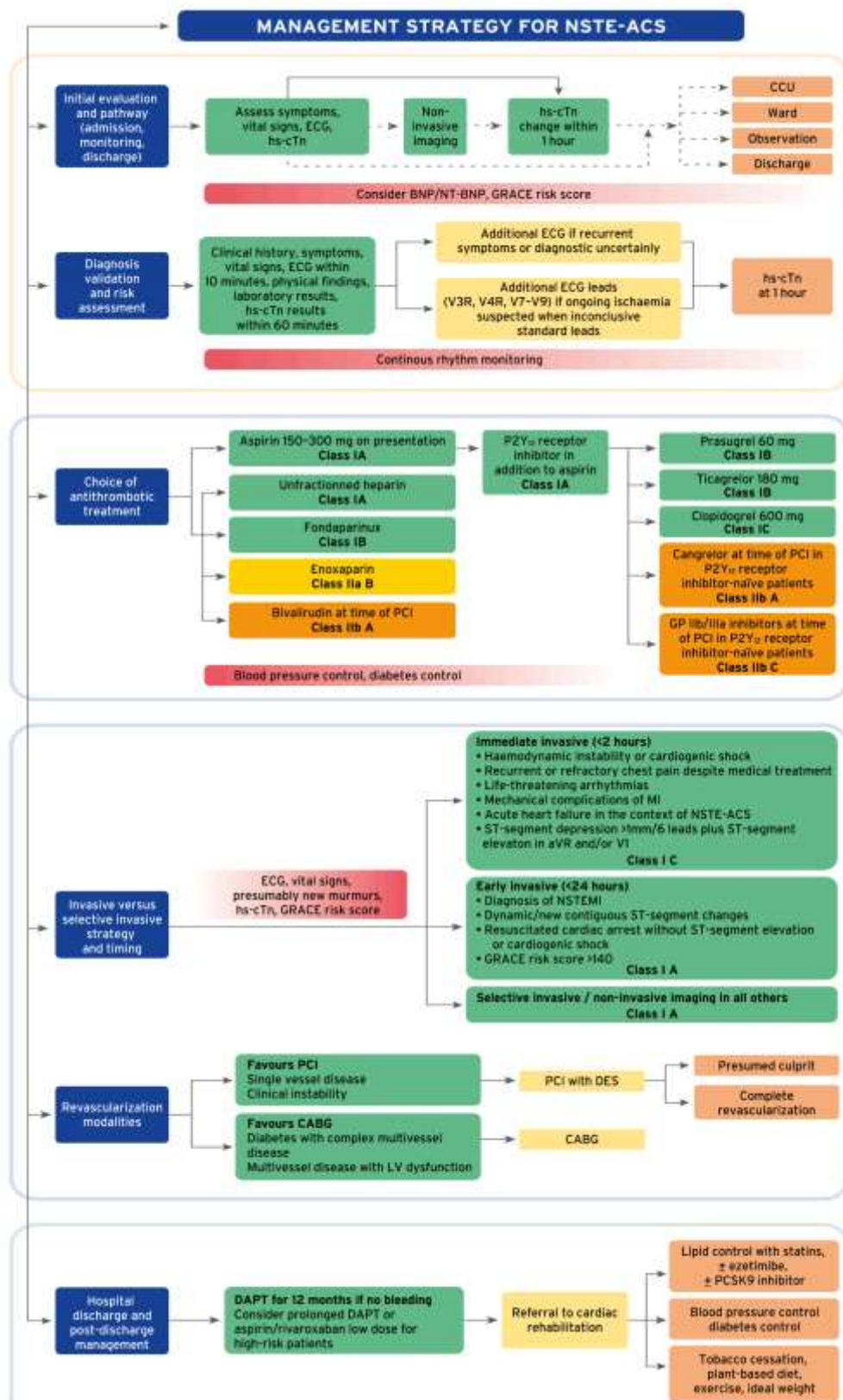


Figure 8-3: Management strategy for NSTEMI-ACS patients. Source: 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

Special populations:

- **Out-of-hospital cardiac arrest (OHCA):**

ACS is the most common cause of OHCA. The management of patients with ROSC without evidence of ST-segment elevation should be individualized according to haemodynamic and neurological status.

In OHCA with an initial shockable rhythm and without ST-elevation or equivalents and without CS, routine immediate ICA is not superior to a delayed invasive strategy (COACT and TOMAHAWK RCTs). It appears reasonable to delay ICA in haemodynamically stable patients with resuscitated OHCA without ST-segment elevation or equivalents. The decision to perform selective coronary angiography (and PCI if indicated) should also consider factors associated with poor neurological outcome and the likelihood of ACS.

Initial evaluation in the ED or ICCU should focus on excluding non-coronary causes (cerebrovascular events, respiratory failure, non-cardiogenic shock, PE, or intoxication).

Echocardiography is also useful in the evaluation of these patients.

Table 8-10: ESC Recommendations for NSTEMI-ACS patients with cardiac arrest and out-of-hospital cardiac arrest:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents).</i> | III | A |
| <i>Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation.</i> | I | B |
| <i>Transport of patients with OHCA to a cardiac arrest centre according to local protocols should be considered.</i> | IIa | C |
| <i>Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest.</i> | I | C |

- **Heart failure and cardiogenic shock:**

30% of acute HF presentations are triggered by ACS, so in patients with ischemic ST abnormality, new Q waves, or severe troponin rise (> 1 ng/ml), MI is presumed the cause of acute HF (type 1 MI) rather the result of it (type 2 MI). An invasive strategy is indicated and multivessel CAD is expected.

In unstable HF patients, such as those with shock or massive pulmonary edema already requiring mechanical ventilation, who also have ongoing deep ST depression, are treated with an immediate invasive strategy within 2 hours ⁽¹⁾.

| Table 8-11: ESC Recommendations for NSTEMI-ACS patients with heart failure or cardiogenic shock: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Immediate coronary angiography and PCI of the IRA (if indicated) is recommended in patients with CS complicating ACS.</i> | I | B |
| <i>Emergency CABG is recommended for patients with CS if the coronary anatomy is not amenable to PCI.</i> | I | B |
| <i>It is recommended to perform emergency echocardiography without delay to assess LV and valvular function and exclude mechanical complications.</i> | I | C |
| <i>In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is recommended, as decided by the Heart Team.</i> | I | C |
| <i>For NSTEMI-ACS-related mechanical complications, the use of IABP should be considered.</i> | IIa | C |

(1) In stable patients, angiography ± PCI are not warranted urgently, as supine positioning and contrast loading during angiography increase preload and aggravate HF, LVEDP and myocardial ischemia. Furthermore, procedural sedation blunts the compensatory vasoconstriction and tachycardia of pre-shock patients. These 3 factors may precipitate a downhill course of shock and massive pulmonary edema requiring urgent intubation in patients who were initially stable. Thus, in somewhat stable patients, coronary angiography is usually performed 1 day later, once proper diuresis has been achieved.

| | | |
|--|------------|----------|
| <i>In selected patients with ACS and CS, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for longterm survival and predicted quality of life.</i> | IIb | C |
| <i>Routine use of IABP in patients with CS and no mechanical complications due to ACS is not recommended.</i> | III | B |

- **Women and ACS:**

- While an initial invasive strategy is not indicated in low-risk men either, a meta-analysis shows that an initial invasive strategy is not harmful to low-risk men but is harmful to low-risk women (higher risk of death/MI with an invasive strategy in RITA 3).
- In addition, women have a higher bleeding risk, particularly at the vascular access site.
- Women also have a higher complication rate with CABG.

- **Patients with cancer:**

- The four most common types of cancer in patients with ACS are prostate, breast, colon, and lung.
- Patients with a history of cancer should be diagnosed and treated like all other ACS patients, but the management of ACS patients with active cancer has some specific issues that need to be taken into consideration:
 - Patients with active cancer presenting with ACS tend to be older, with a larger number of comorbidities and more extensive CAD.
 - As per the ARC-HBR criteria, patients with active cancer diagnosed in the past 12 months are considered as HBR.
 - The management of ACS in patients with cancer can be challenging because of frailty, increased bleeding risk, thrombocytopaenia, and increased thrombotic risk.
 - Given that they are considered to be HBR, the preferred P2Y12 inhibitor for ACS patients with active cancer is clopidogrel.
 - Potential drug–drug interactions with cancer therapies should be checked when using ticagrelor or clopidogrel, since some pharmacokinetic-based drug–drug interactions via CYP450 may occur.

- Following ACS, a review of the cancer medications is recommended, and any cancer drug associated with thrombosis and MI should be stopped.
 - Invasive management in patients with advanced cancer or life expectancy < 6 months has been reported to not demonstrate a mortality benefit compared with a conservative approach.
- **The elderly patients:**
 - One of the major predictors of adverse outcomes following ACS is age, but patients aged ≥ 75 years are often excluded from or under-represented in clinical trials.
 - Hs-cTn assays have an excellent diagnostic performance in the older person, but the specificity of the test is lower than in younger patients.
 - Frail patients with NSTEMI-ACS less frequently receive ACS pharmacotherapies and invasive assessment, have more complex coronary disease, have longer durations of hospital stay, and are at higher risk of death.

| Table 8-12: ESC recommendations for acute coronary syndrome comorbid conditions: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Chronic kidney disease: | | |
| <ul style="list-style-type: none"> ○ Approximately 20-40% of patients presenting with NSTEMI have CKD. ○ Bivalirudin (in patients undergoing PCI) and fondaparinux (outside PCI) are associated with less bleeding than UFH or enoxaparin in patients with mild or moderate renal failure. ○ When GFR is < 30 ml/min, UFH or dose-adjusted enoxaparin are approved for use; the bleeding risk is, however, higher with enoxaparin at any stage of renal failure (GFR < 60 ml/min), and UFH is preferred. | | |
| <i>The use of low- or iso-osmolar contrast media (at the lowest possible volume) is recommended for invasive strategies.</i> | I | A |
| <i>It is recommended to assess kidney function using eGFR in all patients with ACS.</i> | I | C |

| | | |
|---|------------|----------|
| <i>It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as in patients with normal kidney function.</i> | I | C |
| <i>Hydration during and after angiography should be considered in patients at risk of contrast-induced nephropathy, especially in patients with acute kidney injury and/or CKD with eGFR < 30 mL/min/ 1.73 m².</i> | IIa | B |
| Diabetes: | | |
| <i>It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, CKD, and obesity.</i> | I | A |
| <i>It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.</i> | I | B |
| <i>It is recommended to frequently monitor blood glucose levels in patients with known diabetes mellitus or hyperglycaemia (defined as glucose levels ≥ 11.1 mmol/L or ≥ 200 mg/dL).</i> | I | C |
| <i>Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.</i> | IIa | C |
| Older adults: | | |
| <i>It is recommended to apply the same diagnostic and treatment strategies in older patients as in younger patients.</i> | I | B |
| <i>It is recommended to adapt the choice and dosage of antithrombotic agent, as well as of secondary prevention medications, to renal function, co-medications, comorbidities, frailty, cognitive function, and specific contraindications.</i> | I | B |
| <i>For frail older patients with comorbidities, a holistic approach is recommended to individualize interventional and pharmacological treatments after careful evaluation of the risks and benefits.</i> | I | B |
| Patients with cancer: | | |

| | | |
|---|------------|----------|
| <i>An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥ 6 months.</i> | I | B |
| <i>A temporary interruption of cancer therapy is recommended in patients in whom the cancer therapy is suspected to be a contributing cause of ACS ⁽¹⁾.</i> | I | C |
| <i>A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis ⁽²⁾ (i.e. with expected survival < 6 months) and/or very high bleeding risk.</i> | IIa | C |
| <i>Aspirin is not recommended in cancer patients with a platelet count $< 10\,000/\mu\text{L}$.</i> | III | C |
| <i>Clopidogrel is not recommended in cancer patients with a platelet count $< 30\,000/\mu\text{L}$.</i> | III | C |
| <i>In ACS patients with cancer and $< 50\,000/\mu\text{L}$ platelet count, prasugrel or ticagrelor are not recommended.</i> | III | C |

Long-term management of NSTEMI-ACS:

- **Return to regular activities** (including sexual activities) 1-2 weeks after NSTEMI. Patients with a large infarct and new LV dysfunction should avoid strenuous activities for 4 weeks (high arrhythmic risk during this period).
- **long-term management:**

Table 8-13: ESC Recommendations for long-term management after ACS:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Cardiac rehabilitation: | | |
| <i>It is recommended that all ACS patients participate in a medically supervised, structured, comprehensive, multidisciplinary exercise-based cardiac rehabilitation and prevention programme.</i> | I | A |

(1) Anticancer therapies associated with high risk of ACS (very common [$> 10\%$]) include: capecitabine, paclitaxel, cisplatin, carfilzomib, bevacizumab, ramucirumab, aflibercept, axitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, ponatinib, and erlotinib.

(2) Related to advanced cancer stage and/or severe irreversible non-CV comorbidities.

| Lifestyle management: | | |
|--|------------|----------|
| <p><i>It is recommended that ACS patients adopt a healthy lifestyle, including:</i></p> <ul style="list-style-type: none"> - <i>Stopping all smoking of tobacco ⁽¹⁾</i> - <i>Healthy diet (Mediterranean style)</i> - <i>Alcohol restriction (max. 100 g/week; same limit for men and women).</i> - <i>Regular aerobic physical activity and resistance exercise</i> - <i>Reduced sedentary time</i> | I | B |
| <p><i>In smokers, offering follow-up support, nicotine replacement therapy, varenicline or bupropion, individually or in combination, should be considered ⁽²⁾.</i></p> | IIa | A |
| Lipid-lowering drugs: | | |
| <p>Statin therapy should be started during ACS hospitalization regardless of the baseline LDL. Statin's benefit is not usually immediate but may become evident within 1 month. A more immediate benefit is seen in patients undergoing PCI, as high-dose statin reduces peri-PCI MI. Note that, for patients receiving chronic statin therapy, the harm from statin withdrawal is immediate, with an early cardiac risk that is higher than that of statin non-users.</p> | | |
| <p><i>It is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.</i></p> | I | A |
| <p><i>It is recommended to aim to achieve an LDL-C level of < 55 mg/dL (< 1.4 mmol/L) and to reduce LDL-C by ≥ 50% from baseline.</i></p> | I | A |

-
- (1)** Tobacco abstinence is associated with a reduced risk of re-infarction (30-40%) and death (35-45%) after ACS. Interventions for smoking cessation should begin during hospitalization using a combination of behavioural interventions, pharmacotherapy, and counselling. An average weight gain of 5 kg can be expected when a person quits smoking, but it is important to recognize that the CV risk from continued smoking outweighs the CV risk from gaining weight.
- (2)** Drug interventions, including nicotine-replacement therapy (NRT), bupropion and varenicline, should be considered along with behavioural support. All forms of NRT are effective, and the anti-depressant bupropion aids in long-term smoking cessation with similar efficacy to NRT. Varenicline is the most effective medical treatment to support smoking cessation and is safe in ACS patients.

| | | |
|--|------------|----------|
| <i>If the LDL-C goal is not achieved despite maximally tolerated statin therapy after 4-6 weeks, the addition of ezetimibe is recommended.</i> | I | B |
| <i>If the LDL-C goal is not achieved despite maximally tolerated statin therapy and ezetimibe after 4-6 weeks, the addition of a PCSK9 inhibitor is recommended.</i> | I | A |
| <i>It is recommended to intensify lipid-lowering therapy⁽¹⁾ during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission.</i> | I | C |
| <i>For patients with a recurrent atherothrombotic event (recurrence within 2 years of first ACS episode) while taking maximally tolerated statin-based therapy, an LDL-C goal of < 40 mg/dL (< 1.0 mmol/L) may be considered.</i> | IIb | B |
| <i>Combination therapy with high-dose statin plus ezetimibe may be considered during index hospitalization.</i> | IIb | B |
| RAAS system inhibitors: | | |
| <ul style="list-style-type: none"> ○ ACE inhibitors have been demonstrated to improve outcomes in post-MI patients with additional conditions, such as clinical HF and/or LVEF ≤ 40%, diabetes, CKD, and/or hypertension. ○ MRAs reduce short-term (30 days) and long-term mortality when initiated in MI patients with EF < 40%, at 3-7 days (EPHESUS trial). However, its acute initiation in the emergency department in MI with EF > 40% was not beneficial (ALBATROSS trial). | | |
| <i>ACE inhibitors (ARBs in case of intolerance) are recommended in ACS patients with HF symptoms, LVEF ≤ 40%, diabetes, hypertension, and/ or CKD.</i> | I | A |
| <i>Mineralocorticoid receptor antagonists are recommended in ACS patients with an LVEF ≤ 40% and HF or diabetes.</i> | I | A |
| <i>Routine ACE inhibitors for all ACS patients regardless of LVEF should be considered.</i> | IIa | A |
| Beta-blockers: | | |
| <i>The clinical benefit of β-blockers after ACS in patients with reduced LVEF is supported by evidence from contemporary trials. However, the evidence for prescribing β-blockers after uncomplicated ACS in patients with LVEF > 40% is less well established.</i> | | |

(1) Increase statin potency/dose if the patient was on low-potency/low-dose statin, add ezetimibe if the patient was only on statins at highest tolerated dose, or add PCSK9 inhibitor if the patient was on statins plus ezetimibe.

β -blockers significantly reduced the endpoint of death/MI/cardiac arrest between day 2 and day 15, but increased this endpoint in the first day and in unstable patients, making the overall β -blocker effect neutral (COMMIT-CCS trial). Therefore, β -blockers should be avoided on the first day if there are any HF signs or features predictive of cardiogenic shock: SBP < 120 mmHg, heart rate > 110 bpm, or age > 70 years.

| | | |
|---|----------|----------|
| <i>Beta-blockers are recommended in ACS patients with LVEF \leq 40% regardless of HF symptoms.</i> | I | A |
|---|----------|----------|

| | | |
|--|------------|----------|
| <i>Routine beta-blockers for all ACS patients regardless of LVEF should be considered.</i> | IIa | B |
|--|------------|----------|

Proton pump inhibitors:

| | | |
|---|----------|----------|
| <i>Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds.</i> | I | A |
|---|----------|----------|

Imaging:

| | | |
|---|----------|----------|
| <i>In patients with pre-discharge LVEF \leq 40%, repeat evaluation of the LVEF 6-12 weeks after an ACS (and after complete revascularization and the institution of optimal medical therapy) is recommended to assess the potential need for sudden cardiac death primary prevention ICD implantation.</i> | I | C |
|---|----------|----------|

| | | |
|---|------------|----------|
| <i>Cardiac magnetic resonance imaging should be considered as an adjunctive imaging modality in order to assess the potential need for primary prevention ICD implantation.</i> | IIa | C |
|---|------------|----------|

Vaccination

| | | |
|---|----------|----------|
| <i>Influenza vaccination is recommended for all ACS patients.</i> | I | A |
|---|----------|----------|

Anti-inflammatory drugs:

| | | |
|---|------------|----------|
| <i>Low-dose colchicine (0.5 mg once daily) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent CV disease events occur under optimal therapy.</i> | IIb | A |
|---|------------|----------|

N.B: NSAIDs should be avoided for their known risks of renal failure, fluid retention, Hypertension, and GI bleed, especially in combination with aspirin and clopidogrel. If an NSAID is absolutely necessary, use the lowest possible dose and *administer aspirin 2 hours before the NSAID*.

Prognosis:

- In-hospital mortality of NSTEMI is lower than STEMI. However, short-term (30 days) and long-term mortality of NSTEMI approximates STEMI mortality (~3% at 30 days, ~5% at 1 year).
Short-term mortality of unstable angina without positive markers or ST changes is much lower ($\leq 1.7\%$).
- The risk of death or MI is 5-10% at 30 days and ~10-15% at 1 year. The risk is much lower beyond the first year (~2% per year). Half of these events are recurrences at the site of the culprit lesion, while the remaining events are related to non-culprit lesions.

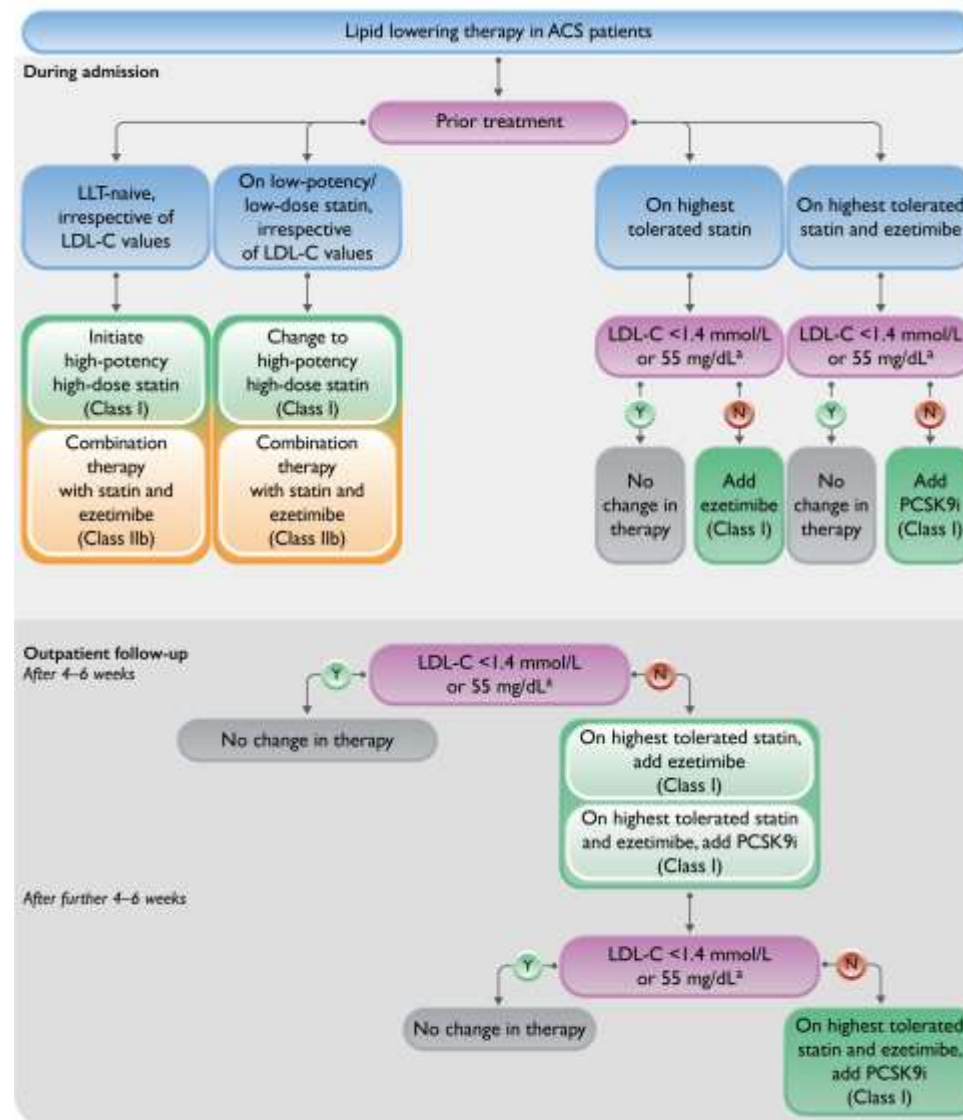


Figure 8-4: Lipid-lowering therapy in ACS patients. Source: 2023 ESC Guidelines for the management of acute coronary syndromes.

Important trials in NSTEMI-ACS:

| Table 8-14: Clinical trials of NSTEMI-ACS: | |
|--|--|
| Trial (date) | Summary |
| Anti-inflammatory drugs: | |
| COLCOT (2019) | <p>Aim: To evaluate the effects of colchicine on CV outcomes as well as its long-term safety profile in patients who had recently had a MI.</p> <p>Study: 4745 patients were randomly assigned within 30 days after a myocardial infarction. to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from CV causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo.</p> |
| Lipid lowering therapy: | |
| PROVE-IT (2004) | <p>Aim: To evaluate the efficacy of standard lipid lowering with pravastatin compared with aggressive lipid lowering using atorvastatin in ACS.</p> <p>Study: 4162 patients who had been hospitalized for ACS within the preceding 10 days and compared pravastatin (40mg daily; standard therapy) with atorvastatin (80 mg daily; intensive therapy). The primary end point was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean follow-up was 24 months. Intensive lipid-lowering statin regimen provides greater protection against death or MACE than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL-C to levels substantially below current target levels.</p> |
| IMPROVE-IT (2015) | <p>Aim: To evaluate the effect of ezetimibe combined with simvastatin, compared with simvastatin alone, in stable patients who had had an ACS and whose LDL-C values were within guideline recommendations.</p> |

| | |
|---------------------------------------|--|
| | <p>Study: 18,144 patients who had been hospitalized for ACS within the preceding 10 days and had LDL-C levels of (50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not receiving lipid-lowering therapy). The combination of simvastatin and ezetimibe was compared with simvastatin alone. The median follow-up was 6 years. When added to statin, ezetimibe resulted in incremental lowering of LDL-C and improved CV outcomes. Moreover, lowering LDL-C to levels below previous targets provided additional benefit.</p> |
| Revascularization in NSTE-ACS: | |
| Timing of invasive strategy: | |
| TACTICS-TIMI-18 (2001) | <p>Aim: To compare early invasive PCI strategy with more conservative, selectively invasive PCI strategy in patients with NSTE-ACS.</p> <p>Study: 2220 patients with NSTE-ACS who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban were randomly assigned to an early invasive strategy, which included routine catheterization within 4 to 48 hours and revascularization as appropriate, or to a more conservative (selectively invasive) strategy, in which catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. The use of an early invasive strategy significantly reduced the incidence of major cardiac events. These data support a policy involving broader use of the early inhibition of glycoprotein IIb/IIIa in combination with an early invasive strategy in such patients.</p> |
| RITA-3 (2002) | <p>Aim: To compare an early invasive approach with a selective invasive approach in patients with NSTE-ACS.</p> <p>Study: 1810 patients with NSTE-ACS were randomly assigned to an early intervention or conservative strategy. The antithrombin agent in both groups was enoxaparin. The co-primary endpoints were a combined rate of death, non-fatal MI, or refractory angina at 4 months; and a combined rate of death or non-fatal MI at 1 year. The interventional strategy is preferable to a conservative strategy, mainly because of the halving of refractory or severe angina, and with no increased risk of death or MI.</p> |
| FRISC-II (2016) | <p>Aim: To evaluate treatment with an early invasive strategy compared with a conservative management strategy on late clinical events.</p> |

| | |
|--|--|
| | <p>Study: 2457 patients with NSTEMI-ACS were randomly assigned to an early invasive treatment strategy, aiming for revascularisation within 7 days, or a non-invasive strategy, with invasive procedures at recurrent symptoms or severe exercise-induced ischaemia. The primary endpoint was a composite of death or MI. During 15 years of follow-up, an early invasive treatment strategy postponed the occurrence of death or next MI by an average of 18 months, and the next readmission to hospital for ischaemic heart disease by 37 months, compared with a non-invasive strategy in patients with NSTEMI-ACS. This remaining lifetime perspective supports that an early invasive treatment strategy should be the preferred option in most patients with NSTEMI-ACS.</p> |
| ABOARD (2009) | <p>Aim: To evaluate a strategy of catheterization and revascularization immediately after admission for NSTEMI-ACS.</p> <p>Study: 352 patients with NSTEMI-ACS and a TIMI score of 3 or more to receive intervention either immediately or on the next working day (between 8 and 60 hours after enrollment). The primary end point was the peak troponin value during hospitalization. A strategy of immediate intervention compared with a strategy of intervention deferred to the next working day (mean, 21 hrs) did not result in a difference in MI as defined by peak troponin level.</p> |
| EARLY (2018) | <p>Aim: To assess the safety and efficacy of a very early invasive strategy compared with a delayed invasive strategy among patients with intermediate-to high-risk NSTEMI-ACS who were not pretreated with a P2Y2 inhibitors.</p> <p>Study: 1142 patients with intermediate-to high-risk NSTEMI-ACS who were not pretreated with a P2Y2 inhibitors were randomized to very early invasive approach (within 2 hours) or delayed invasive strategy (12-72 hours). The primary outcome of cardiovascular (CV) death or recurrent ischemia at 30 days. very early invasive strategy is superior to a delayed invasive strategy in improving symptoms of recurrent ischemia. No differences in hard endpoints such as CV death or MI were noted.</p> |
| Complete revascularization in NSTEMI-ACS: | |
| CULPRIT-SHOCK (2017) | <p>Aim: To assess safety and efficacy of culprit-lesion-only PCI versus multivessel PCI among patients presenting with acute MI and cardiogenic shock in the setting of multivessel disease.</p> |

| | |
|---|---|
| | <p>Study: 706 patients who had multivessel disease, AMI, and cardiogenic shock were randomly assigned to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. The primary end point was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. The 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent immediate multivessel PCI.</p> |
| SMILE (2016) | <p>Aim: To compare long-term outcomes of one stage PCI during index procedure or multistage PCI during index hospitalization in patients with NSTEMI and multivessel coronary artery disease.</p> <p>Study: 584 patients were randomly assigned to 1-stage percutaneous coronary intervention (1S-PCI) during the index procedure versus multistage percutaneous coronary intervention (MS-PCI) complete coronary revascularization during the index hospitalization. The primary study endpoint was the incidence of MACCE at 1 year. In multivessel NSTEMI patients, complete 1-stage coronary revascularization is superior to multistage PCI in terms of major adverse cardiovascular and cerebrovascular events.</p> |
| BIOVASC (2023) | <p>Aim: To investigate whether PCI for non-culprit lesions should be attempted during the index procedure or staged.</p> <p>Study: 764 patients with STEMI or NSTEMI-ACS and multivessel coronary artery disease with a clearly identifiable culprit lesion. A were randomly assigned to undergo immediate complete revascularisation or staged complete revascularisation (PCI of only the culprit lesion during the index procedure and PCI of all non-culprit lesions within 6 weeks after the index procedure). The primary outcome was the composite of all-cause mortality, MI, any unplanned ischaemia-driven revascularisation, or cerebrovascular events at 1 year after the index procedure. In patients presenting with ACS and multivessel disease, immediate complete revascularisation was non-inferior to staged complete revascularisation for the primary composite outcome and was associated with a reduction in MI and unplanned ischaemia-driven revascularisation.</p> |
| <p>Out of hospital cardiac arrest:</p> | |

| | |
|----------------------------|---|
| COACT (2019) | <p>Aim: <i>To assess if a strategy of immediate coronary angiography (and PCI if necessary) would be better than a strategy of delayed angiography in patients who are successfully resuscitated after cardiac arrest in the absence of STEMI, with respect to overall survival.</i></p> <p>Study: <i>552 patients who had cardiac arrest without signs of STEMI were randomly assigned to undergo immediate coronary angiography or coronary angiography that was delayed until after neurologic recovery. All patients underwent PCI if indicated. The primary end point was survival at 90 days. Immediate angiography was not found to be better than delayed angiography with respect to overall survival at 90 days.</i></p> |
| TOMAHAWK (2021) | <p>Aim: <i>To test the hypothesis that routine immediate coronary angiography (and PCI if necessary) is superior to a deferred or selective approach regarding 30-day all-cause mortality in resuscitated patients with out-of-hospital cardiac arrest without ST-segment elevation.</i></p> <p>Study: <i>554 patients with successfully resuscitated out-of-hospital cardiac arrest of possible coronary origin were randomly assigned to undergo either immediate coronary angiography or initial intensive care assessment with delayed or selective angiography. All the patients had no evidence of ST-segment elevation on postresuscitation electrocardiography. The primary end point was death from any cause at 30 days. A strategy of immediate angiography provided no benefit over delayed or selective strategy with respect to the 30-day all-cause mortality.</i></p> |

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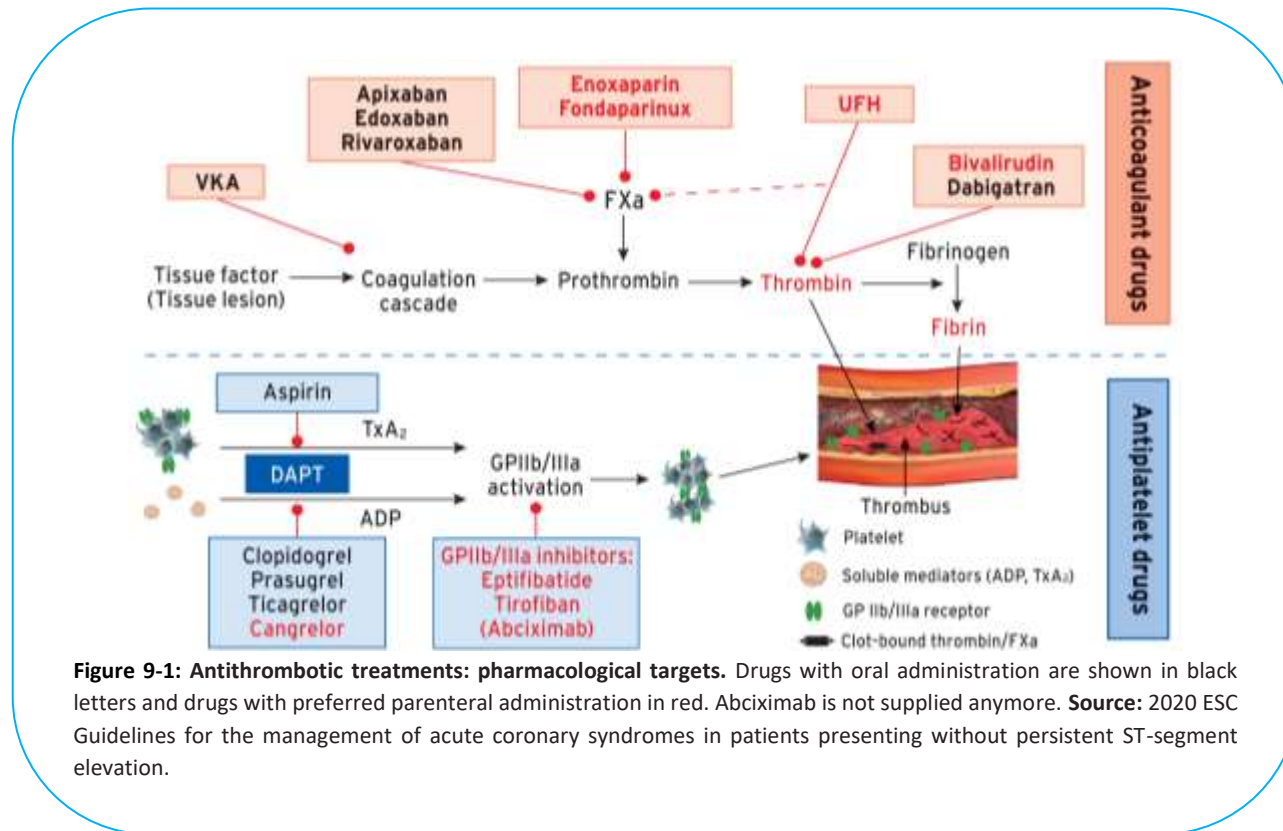
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Chapter 9:

Antithrombotic Therapy in Ischemic Heart Diseases



Antithrombotic therapy in Acute Coronary Syndrome

Antithrombotic treatment is an important component of the management of all patients presenting with ACS. The specific choice and combination of therapy, the time of its initiation, and the treatment duration depend on various patient and procedural

factors. Treatment decisions must be made weighing the benefits of antithrombotic therapy against the risk of bleeding, including severe, life-threatening bleeding.

Antithrombotic therapy in the acute phase

Antiplatelet therapy:

- **Oral antiplatelet therapy:**

- Aspirin treatment is started with a loading dose as soon as possible, followed by maintenance dose of 75-100 mg once daily.
- DAPT including aspirin and a potent P2Y₁₂ inhibitor (prasugrel or ticagrelor) is recommended as the default DAPT strategy for ACS patients (PLATO and TRITON-TIMI 38 studies).
- Prasugrel should be considered in preference to ticagrelor for ACS patients who proceed to PCI (ISAR-REACT 5 RCT).
- Clopidogrel, which is characterized by less effective and more variable platelet inhibition, should only be used: **(1)** when prasugrel or ticagrelor are contraindicated/not available, or **(2)** in some patients considered at HBR (e.g., ≥ 1 major or ≥ 2 minor ARC-HBR criteria), **(3)** in older patients (e.g., ≥ 70 years).
- Timing of loading dose: Both aspirin and oral P2Y₁₂ inhibitors achieve platelet inhibition more rapidly following oral loading dose. Pre-treatment refers to a strategy in which an antiplatelet drug, usually a P2Y₁₂ inhibitor, is given before coronary angiography and, therefore, before the coronary anatomy is known. Although a potential benefit with pre-treatment in the setting of ACS has been hypothesized, large randomized trials supporting a routine pre-treatment strategy with P2Y₁₂ inhibitors are lacking.
 - In patients with STEMI undergoing PPCI, pre-treatment with a P2Y₁₂ inhibitor may be considered.
 - In patients with NSTEMI-ACS, routine pre-treatment with a P2Y₁₂ inhibitor before knowing the coronary anatomy in patients anticipated to undergo an early invasive strategy (i.e. < 24 h) is not recommended.
 - For patients with NSTEMI-ACS, where there is anticipated delay to invasive angiography (i.e. > 24 h), pre-treatment with a P2Y₁₂ inhibitor may be considered according to the bleeding risk of the patient.
 - In all ACS patients proceeding to PCI who did not receive P2Y₁₂ inhibitor pre-treatment, loading dose is recommended at the time of PCI.

- **Intravenous antiplatelet drugs:**

- Glycoprotein (GP) IIb/IIIa inhibitors should be considered in PCI-treated ACS patients for: **(1)** bailout if there is evidence of no-reflow or a thrombotic complication during PCI, **(2)** high-risk PCI in patients who have not been pre-treated with P2Y12 receptor inhibitors.
- Cangrelor may be considered in P2Y12 receptor inhibitor-naïve ACS patients undergoing PCI, including patients for whom it may not be feasible to give oral drugs in the setting of emergent PCI (e.g., CS patients and/or patients on mechanical ventilation).

Anticoagulant treatment:

- Anticoagulation is an important component of the initial treatment of ACS and the peri-procedural treatment for ACS patients managed with invasive strategy.
- In general, a crossover between anticoagulants should be avoided in patients with ACS (especially between unfractionated heparin and LMWH), with the exception of adding UFH to fondaparinux when a patient presenting with NSTEMI-ACS proceeds to PCI after a period of fondaparinux treatment.
- Anticoagulants should generally be discontinued immediately after PCI, except in specific clinical settings such as: **(1)** the confirmed presence of LV aneurysm with thrombus formation or **(2)** AF requiring anticoagulation, **(3)** for bivalirudin in patients with STEMI undergoing PCI, a full dose post-PCI infusion is recommended.
- **Anticoagulation in patients with STEMI undergoing primary PCI:** parenteral anticoagulation is recommended and UFH is the default choice of anticoagulant. Enoxaparin and bivalirudin should be considered as alternatives to UFH in these patients but fondaparinux is not recommended ⁽¹⁾.
- **Anticoagulation in patients with NSTEMI-ACS undergoing angiography and PCI if indicated:**
 - For patients with NSTEMI-ACS undergoing immediate or early angiography (\pm PCI if indicated), UFH is recommended but enoxaparin should be considered as an alternative to UFH.

(1) Guiding catheter thrombus formation was of concern with fondaparinux.

- For patients with NSTEMI-ACS who are not anticipated to undergo early angiography, fondaparinux (with a UFH bolus at time of PCI) is recommended in preference to enoxaparin (OASIS-5 trial). Enoxaparin should be considered if fondaparinux is not available.

Antithrombotic therapy as an adjunct to fibrinolysis:

- The first dose of aspirin (162–325 mg) should be chewed or given i.v. and a low dose (75-100 mg) given orally daily from the next day thereafter.
- Clopidogrel added to aspirin reduces the risk of CV events and overall mortality in patients treated with fibrinolysis. Based on the available RCTs, there is insufficient evidence to support or refute improved outcomes with ticagrelor or prasugrel in patients with STEMI treated with thrombolytics.
- There is no evidence that administration of GP IIb/IIIa receptor inhibitors improves myocardial perfusion or outcomes in patients treated with fibrinolysis, and it may increase the risk of bleeding.
- Parenteral anticoagulation is recommended until revascularization, if performed. Despite an increased risk of major bleeding, the net clinical benefit favoured enoxaparin over UFH (ASSENT 3, ExTRACT-TIMI 25). Fondaparinux was superior to UFH in preventing death and re-infarction (OASIS-6 trial).

Antithrombotic therapy in patients not undergoing reperfusion:

- Potent P2Y₁₂ inhibitor-based DAPT is a reasonable option, unless concerns over the bleeding risk prevail (e.g. based on ARC-HBR criteria).
- A DAPT regimen based on clopidogrel and aspirin may provide a good net clinical benefit among older ACS patients.

Maintenance Antithrombotic therapy strategies

First 12 months after revascularization:

- **Anticoagulation:** Continuation after PCI is not necessary, unless used for another indication.

- **Antiplatelet therapy:** Following PCI, a default DAPT regimen consisting of aspirin and a potent P2Y12 inhibitor (prasugrel or ticagrelor) is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. Antiplatelet strategies to reduce bleeding risk in the first 12 months after ACS can be divided into abbreviated DAPT strategies and DAPT de-escalation strategies:
 - **Abbreviated DAPT ⁽¹⁾:**
 - DAPT abbreviation strategies (followed preferably by P2Y12 inhibitor monotherapy within the first 12 months post-ACS) should be considered in patients who are event-free after 3-6 months of DAPT and who are not high ischemic risk, with the duration of DAPT guided by the ischemic and bleeding risks.
 - For high bleeding risk (HBR) patients, aspirin or P2Y12 inhibitor monotherapy after 1 month of DAPT may be considered.
 - **De-escalation strategy:**

P2Y12 inhibitor de-escalation (i.e. switching from prasugrel/ ticagrelor to clopidogrel) in ACS patients may be considered as an alternative strategy to the default treatment regimen in order to reduce the risk of bleeding events. However, it is important to note that there is a potential risk of increased ischaemic events with de-escalation and this strategy is not recommended in the first 30 days after the index ACS event.

(1) *Several RCTs and meta-analyses have compared standard 12-month DAPT with ≤ 6 months DAPT followed by aspirin monotherapy in ACS patients. In some of these trials, the reduction in bleeding events associated with abbreviated DAPT regimens came at the cost of an increase in the rates of ischaemic complications. In a large-scale network meta-analysis, 3-month DAPT was associated with higher rates of MI or stent thrombosis in ACS patients. It should be noted that much of the evidence on these strategies in ACS patients is derived from trials powered primarily for bleeding outcomes, many of which had a non-inferiority design and were, therefore, not powered to detect potentially relevant differences in ischemic outcomes. The patient populations enrolled in these studies were also often relatively selected, often excluding or under-representing the highest risk ACS patients. These important limitations explain why these strategies should at present remain considered as alternative strategies to the default of 12 months DAPT.*

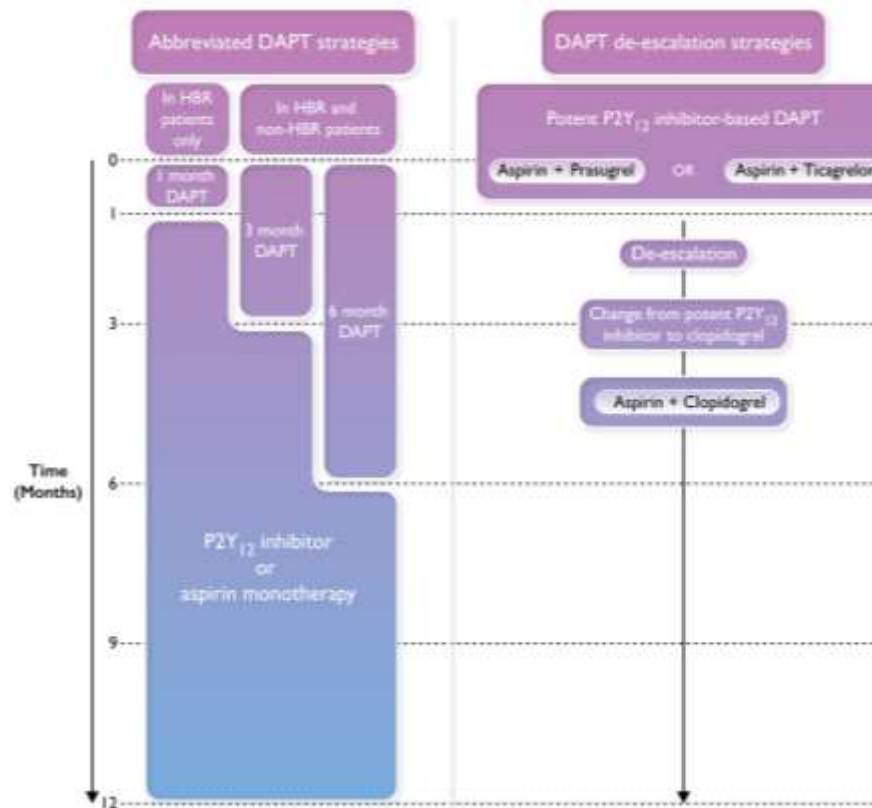


Figure 9-2: Antiplatelet strategies to reduce bleeding risk in the first 12 months after ACS. Source: 2023 ESC guidelines for management of acute coronary syndromes.

Long-term treatment:

- Prolonging antithrombotic therapy beyond 12 months: **(i)** should be considered in those with high thrombotic risk and without an increased risk of major or life-threatening bleeding, and **(ii)** may be considered in ACS patients with moderately elevated thrombotic risk who have tolerated DAPT without a bleeding complication.

- **Prolonging antithrombotic therapy beyond 12 months has two strategies:**
 - Prolonging DAPT based on the results of the PEGASUS-TIMI 54 and DAPT trials. Of note, ticagrelor (60 mg b.i.d.) was associated with reduced bleeding compared with the 90 mg b.i.d. dose and should be preferred for extended therapy > 12 months.
 - Dual antithrombotic therapy [consisting of rivaroxaban (2.5 mg b.i.d.) in combination with aspirin] based on the COMPASS trial (62% of patients had a history of MI).

| Table 9-1: Risk criteria for extended treatment with a second antithrombotic agent | |
|--|--|
| High thrombotic risk (Class IIa) | Moderate thrombotic risk (Class IIb) |
| Complex CAD and at least one criterion: | Non-complex CAD and at least one criterion: |
| Risk enhancers: | |
| <ul style="list-style-type: none"> ○ Diabetes mellitus requiring medication ○ History of recurrent MI ○ Polyvascular disease (CAD plus PAD) ○ CKD with eGFR 15–59 mL/min/1.73 m² | |
| <ul style="list-style-type: none"> ○ Any multivessel CAD ○ Premature (< 45 years) or accelerated (new lesion within a 2-year timeframe) CAD ○ Concomitant systemic inflammatory disease (e.g. HIV, SLE, chronic arthritis) | |
| Technical aspects: | |
| <ul style="list-style-type: none"> ○ At least three stents implanted ○ At least three lesions treated ○ Total stent length > 60 mm | |

- History of complex revascularization (left main, bifurcation stenting with ≥ 2 stents implanted, chronic total occlusion, stenting of last patent vessel) History of stent thrombosis on antiplatelet treatment

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgment with knowledge of the patient's cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients and on data from related registries.

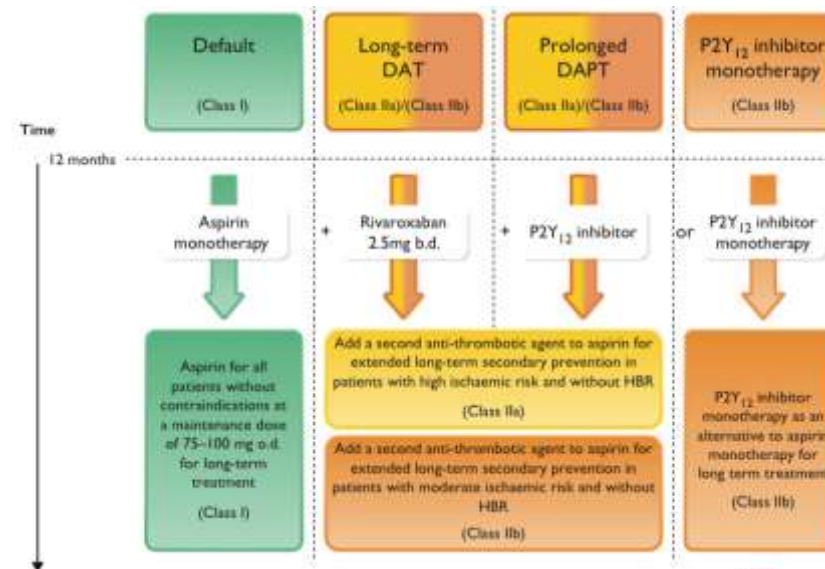


Figure 9-3: Antithrombotic strategies beyond the first 12 months after ACS. DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; HBR, high bleeding risk; MD, maintenance dose; o.d., once a day. **Source:** 2023 ESC guidelines for management of acute coronary syndromes, supplementary data.

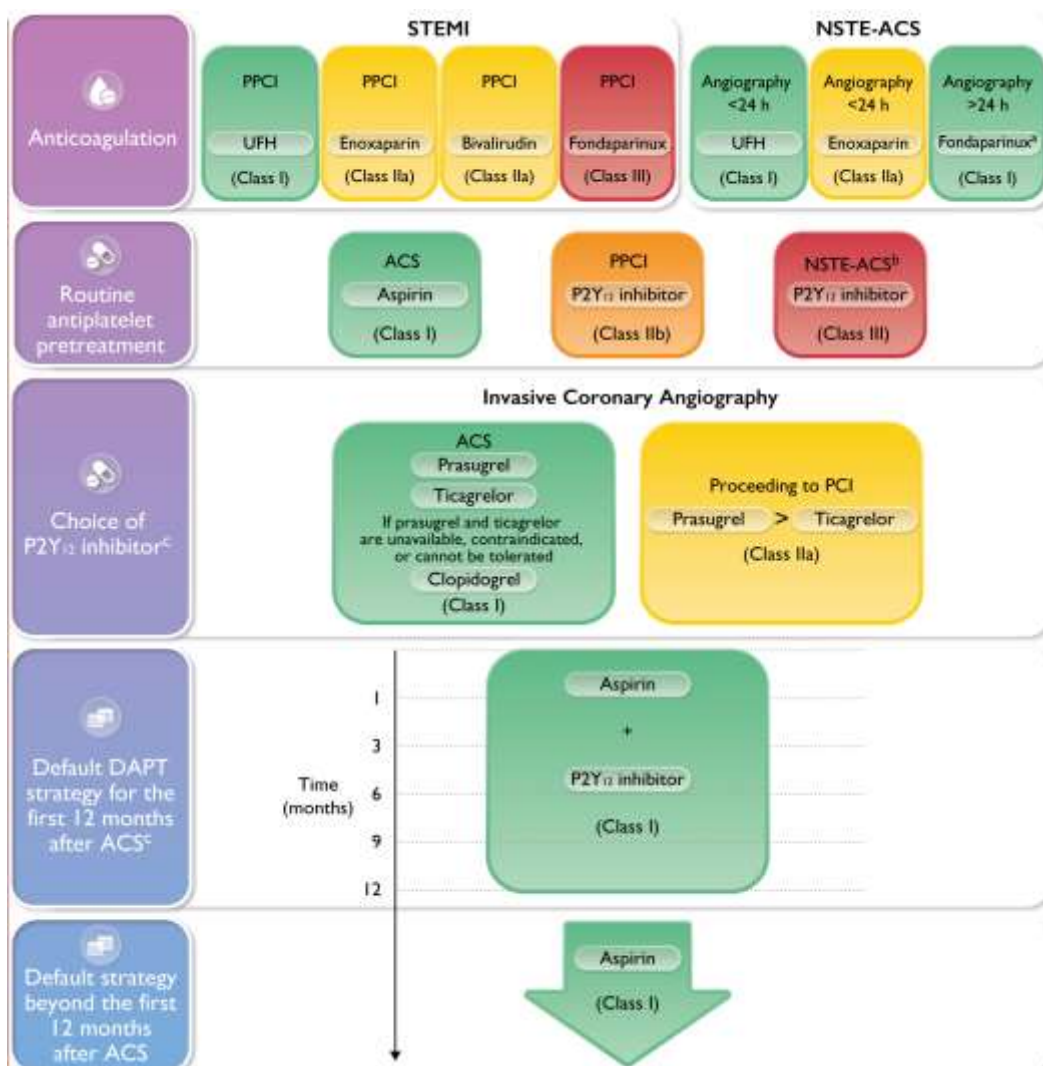


Figure 9-4: Recommended default antithrombotic therapy regimens in ACS patients without an indication for oral anticoagulation. (A) Fondaparinux (plus a single bolus of UFH at the time of PPCI) is recommended in preference to enoxaparin for NSTEMI-ACS patients in cases of medical treatment or logistical constraints for transferring the NSTEMI-ACS patient to PPCI within 24 h of symptom onset. **(B)** Routine pre-treatment with a P2Y₁₂ receptor inhibitor in NSTEMI-ACS patients in whom coronary anatomy is not known and early invasive management (< 24 h) is planned is not recommended, but pre-treatment with a P2Y₁₂ receptor inhibitor may be considered in NSTEMI-ACS patients who are not expected to undergo an early invasive strategy (< 24 h) and do not have HBR. **(C)** Clopidogrel is recommended for 12 months DAPT if prasugrel and ticagrelor are not available, cannot be tolerated, or are contraindicated, and may be considered in older ACS patients (typically defined as older than 70–80 years of age). **Source:** 2023 ESC guidelines for management of acute coronary syndromes.

Table 9-2: ESC Recommendations on antithrombotic therapy in acute coronary syndrome:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Antiplatelet therapy: | | |
| <i>Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.) and an MD of 75–100 mg o.d. for long-term treatment.</i> | I | A |
| <i>In all ACS patients, a P2Y12 receptor inhibitor is recommended in addition to aspirin, given as an initial oral LD followed by an MD for 12 months unless there is HBR.</i> | I | A |
| <i>A proton pump inhibitor in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.</i> | I | A |
| <i>Prasugrel is recommended in P2Y12 receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg o.d. MD, 5 mg o.d. MD for patients aged ≥ 75 years or with a BW < 60 kg).</i> | I | B |
| <i>Ticagrelor is recommended irrespective of the treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d. MD).</i> | I | B |
| <i>Clopidogrel (300–600 mg LD, 75 mg o.d. MD) is recommended when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.</i> | I | C |
| <i>If patients presenting with ACS who stop DAPT to undergo CABG, it is recommended they resume DAPT after surgery for at least 12 months.</i> | I | C |
| <i>Prasugrel should be considered in preference to ticagrelor for ACS patients who proceed to PCI.</i> | IIa | B |
| <i>GP IIb/IIIa receptor antagonists should be considered if there is evidence of no-reflow or a thrombotic complication during PCI.</i> | IIa | C |
| <i>In P2Y12 receptor inhibitor-naïve patients undergoing PCI, cangrelor may be considered.</i> | IIb | A |

| | | |
|--|------------|----------|
| <i>In older ACS patients ⁽¹⁾, especially if HBR ⁽²⁾, clopidogrel as the P2Y12 receptor inhibitor may be considered.</i> | IIb | B |
| <i>Pre-treatment with a P2Y12 receptor inhibitor may be considered in patients undergoing a primary PCI strategy.</i> | IIb | B |
| <i>Pre-treatment with a P2Y12 receptor inhibitor may be considered in NSTEMI-ACS patients who are not expected to undergo an early invasive strategy (< 24 h) and do not have HBR.</i> | IIb | C |
| <i>Routine pre-treatment with a P2Y12 receptor inhibitor in NSTEMI-ACS patients in whom coronary anatomy is not known and early invasive management (< 24 h) is planned is not recommended.</i> | III | A |
| <i>Pre-treatment with a GP IIb/IIIa receptor antagonist is not recommended.</i> | III | A |
| Anticoagulant therapy: | | |
| <i>Parenteral anticoagulation is recommended for all patients with ACS at the time of diagnosis.</i> | I | A |
| <i>Routine use of a UFH bolus (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg) is recommended in patients undergoing PCI.</i> | I | C |
| <i>Intravenous enoxaparin at the time of PCI should be considered in patients pre-treated with subcutaneous enoxaparin.</i> | IIa | B |
| <i>Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.</i> | IIa | C |
| Patients with STEMI: | | |
| <i>Enoxaparin should be considered as an alternative to UFH in patients with STEMI undergoing PPCI.</i> | IIa | A |
| <i>Bivalirudin with a full-dose post PCI infusion should be considered as an alternative to UFH in patients with STEMI undergoing PPCI.</i> | IIa | A |

(1) The definition of older patients varies across trials, ranging from 70 to 80 years of age. Frailty and comorbidities should also be taken in consideration.

(2) HBR should be assessed in a structured manner, e.g. presence of a single major or two minor characteristics defined by ARC-HBR.

| | | |
|---|------------|----------|
| <i>Fondaparinux is not recommended in patients with STEMI undergoing PPCI.</i> | III | B |
| Patients with NSTEMI-ACS: | | |
| <i>For patients with NSTEMI-ACS in whom early invasive angiography (i.e. within 24 h) is not anticipated, fondaparinux is recommended.</i> | I | B |
| <i>For patients with NSTEMI-ACS in whom early invasive angiography (i.e. within 24 h) is anticipated, enoxaparin should be considered as an alternative to UFH.</i> | IIa | B |
| Shortening/de-escalation of antithrombotic therapy: | | |
| <i>In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a P2Y₁₂ receptor inhibitor) should be considered.</i> | IIa | A |
| <i>De-escalation of P2Y₁₂ inhibitor treatment (e.g. with a switch from prasugrel/ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy to reduce bleeding risk.</i> | IIb | A |
| <i>In HBR patients, aspirin or P2Y₁₂ receptor inhibitor monotherapy after 1 month of DAPT may be considered.</i> | IIb | B |
| <i>De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.</i> | III | B |
| Prolonging antithrombotic therapy: | | |
| <i>Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.</i> | I | B |
| <i>Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with high ischaemic risk and without HBR ⁽¹⁾.</i> | IIa | A |

(1) The evidence supporting this approach (prolonged treatment with a second antithrombotic agent) is based on trials in which the duration of prolonged treatment was as follows: mean of 23 months (COMPASS), mean of 18 months (DAPT trial), and median of 33 months (PEGASUS-TIMI 54). Therefore, the benefits and risks associated with continuation of these respective treatments beyond these time points is at present unclear.

| | | |
|--|------------|----------|
| <i>Antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderate ischaemic risk and without HBR.</i> | IIb | A |
| <i>P2Y12 inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.</i> | IIb | A |

Table 9-3: Dose regimen of antiplatelet and anticoagulant drugs in ACS patients ⁽¹⁾:

Antiplatelet drugs:

| | |
|--|--|
| Aspirin | <ul style="list-style-type: none"> - Loading dose (LD) of 150-300 mg orally <u>or</u> 75-250 mg i.v. if oral ingestion is not possible, followed by oral maintenance dose (MD) of 75-100 mg o.d. - No specific dose adjustment in CKD patients. |
| P2Y12 receptor inhibitors (oral or i.v.): | |
| Clopidogrel | <ul style="list-style-type: none"> - LD of 300-600 mg orally, followed by a MD of 75 mg o.d. - No specific dose adjustment in CKD patients. - At the time of fibrinolysis: initial dose of 300 mg (75 mg for patients > 75 years of age). |
| Prasugrel | <ul style="list-style-type: none"> - LD of 60 mg orally, followed by a MD of 10 mg o.d. (reduced to 5 mg o.d. if BW < 60 kg). - In patients aged ≥ 75 years, prasugrel should be used with caution, but a dose of 5 mg o.d. should be used if treatment is deemed necessary. - No specific dose adjustment in CKD patients. - Prior stroke is a contraindication for prasugrel. |
| Ticagrelor | <ul style="list-style-type: none"> - LD of 180 mg orally, followed by a MD of 90 mg b.i.d. - No specific adjustment in CKD patients. |

(1) All dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

| | |
|---|--|
| Cangrelor | <ul style="list-style-type: none"> - Bolus of 30 mcg/kg i.v. followed by 4 mcg/kg/min infusion for at least 2 h or the duration of the procedure (whichever is longer). - In the transition from cangrelor to a thienopyridine, the thienopyridine should be administered immediately after discontinuation of cangrelor with an LD (clopidogrel 600 mg or prasugrel 60 mg); to avoid a potential DDI, prasugrel may also be administered 30 min before the cangrelor infusion is stopped. - Ticagrelor (LD 180 mg) should be administered at the time of PCI to minimize the potential gap in platelet inhibition during the transition phase. |
| GP IIb/IIIa receptor inhibitors (i.v.): | |
| Abciximab | Bolus of 0.25 mg/kg i.v. and 0.125 mcg/kg/min infusion (max 10 mcg/min) for 12 h (drug is not supplied anymore). |
| Eptifibatide | <ul style="list-style-type: none"> - Double bolus of 180 mcg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 mcg/kg/min for up to 18 h. - For CrCl 30-50 mL/min: first LD, 180 mcg/kg i.v. bolus (max 22.6 mg); maintenance infusion, 1 mcg/kg/min (max 7.5 mg/h). Second LD (if PCI), 180 mcg/kg i.v. bolus (max 22.6 mg) should be administered 10 min after the first bolus. - Contraindicated in patients with end-stage renal disease and with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or platelet count < 100 000/mm³. |
| Tirofiban | <ul style="list-style-type: none"> - Bolus of 25 mcg/kg i.v. over 3 min, followed by infusion 0.15 mcg/kg/min for up to 18 h. - For CrCl ≤ 60 mL/min: LD, 25 mcg/kg i.v. over 5 min followed by a maintenance infusion of 0.075 mcg/kg/min continued for up to 18 h. - Contraindicated in patients with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or platelet count < 100 000/mm³. |
| Anticoagulant drugs (for use before and during PCI): | |

| | |
|---------------------|---|
| UFH | <ul style="list-style-type: none"> - Initial treatment: i.v. bolus 70-100 U/kg then infusion titrated to achieve aPTT of 60-80s. - During PCI: 70–100 U/kg i.v. bolus <u>or</u> according to ACT in case of UFH pre-treatment. |
| Enoxaparin | <ul style="list-style-type: none"> - Initial treatment: for treatment of ACS 1 mg/kg b.i.d. subcutaneously for a minimum of 2 days and continued until clinical stabilization. - In patients whose CrCl < 30 mL/min (by Cockcroft–Gault equation), the dosage should be reduced to 1 mg/kg o.d. - During PCI: for patients managed with PCI, if the last dose of enoxaparin was given less than 8 h before balloon inflation, no additional dosing is needed. - If the last s.c. administration was given more than 8 h before balloon inflation, an i.v. bolus of 0.3 mg/kg enoxaparin sodium should be administered. |
| Bivalirudin | <ul style="list-style-type: none"> - During PPCI: 0.75 mg/kg i.v. bolus followed by 1.75 mg/kg/h for 4 h after the procedure. - In patients whose CrCl < 30 mL/min (by Cockcroft–Gault equation), maintenance infusion should be reduced to 1 mg/kg/h. |
| Fondaparinux | <ul style="list-style-type: none"> - Initial treatment: 2.5 mg/d subcutaneously. - During PCI: A single bolus of UFH is recommended. - Avoid if CrCl < 20 mL/min. |

Table 9-4: Major and minor criteria for high bleeding risk according to the Academic Research Consortium (ARC-HBR):

| Bleeding risk is high if at least one major <u>or</u> two minor criteria are met: | |
|---|--|
| Major | Minor |
| <ul style="list-style-type: none"> - Anticipated use of long-term OAC ⁽¹⁾ - Severe or end-stage CKD (eGFR < 30 mL/min) - Haemoglobin < 11 g/dL - Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent - Baseline thrombocytopenia (plt < 100 x 10⁹/L) ⁽²⁾ - Chronic bleeding diathesis - Liver cirrhosis with portal hypertension - Active malignancy ⁽³⁾ (excluding non-melanoma skin cancer) within the past 12 months. - Previous spontaneous intracranial haemorrhage - Previous traumatic intracranial haemorrhage within the past 12 months - Presence of a brain arteriovenous malformation | <ul style="list-style-type: none"> - Age ≥ 75 years - Moderate CKD (eGFR 30-59 mL/min) - Hb 11-12.9 g/dL for men or 11-11.9 g/dL for women - Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion. - Chronic use of oral NSAIDs or steroids - Any ischaemic stroke at any time not meeting the major criterion. |

(1) This excludes vascular protection doses.

(2) Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

(3) Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy)

- | | |
|--|--|
| <ul style="list-style-type: none"> - Moderate or severe ischaemic stroke ⁽¹⁾ within the past 6 months - Major surgery or major trauma within 30 days prior to PCI - Non-deferrable major surgery on DAPT | |
|--|--|

Antiplatelet therapy in patients requiring oral anticoagulation

- **Before PCI:**

- It is unknown whether it is safer to bridge NOACs with parenteral anticoagulants or to continue NOACs without additional parenteral anticoagulation.
- In VKA-treated patients, no parenteral anticoagulation is needed if the INR is > 2.5.

- **After PCI:**

- **Default strategy:**

- Triple antithrombotic (with OAC and DAPT consisting of aspirin and clopidogrel ⁽²⁾) for up to 1 week ⁽³⁾.
- Followed by Dual Antithrombotic with OAC and SAPT (preferably clopidogrel) for up to 12 months.
- Beyond 12 months, it is recommended to stop antiplatelet therapy and continue with OAC monotherapy in most patients (AFIRE trial).

- **Dose of OAC:**

- NOAC should be taken at the recommended dose for stroke prevention.
- In patients treated with VKA, the intensity of OAC should be carefully monitored with a target INR of 2.0–2.5 (except individuals with a mechanical prosthetic valve in the mitral position).

- **Regarding duration of TAT and DAT:**

(1) National Institutes of Health Stroke Scale score > 5.

(2) In the absence of robust safety and efficacy data, the use of prasugrel or ticagrelor as part of TAT is not recommended.

(3) The up to 1 week duration of TAT is based on the median treatment duration in the investigational arm of the AUGUSTUS trial.

- **In patients with multiple HBR factors:** DAT may be shortened to 6 months.
- **In patients with high ischemic risk** or other anatomical/procedural characteristics that outweigh the bleeding risk, TAT should be prolonged for up to 1 month, followed by DAT for up to 12 months.
- **In medically managed ACS patients:** current data support DAT over TAT, with a single antiplatelet agent (most commonly clopidogrel) for at least 6 months.
- **In ACS patients undergoing CABG with an indication for OAC:** anticoagulation in combination with SAPT should be resumed after CABG as soon as possible and TAT should be avoided.
- **In patients with STEMI managed with thrombolytics:** Thrombolytic therapy may be associated with an increased risk of bleeding in systemically anticoagulated patients. Therefore, the initial step should be to assess the anticoagulation status (e.g. INR in a patient taking VKA; with a NOAC, assessing, for example, aPTT on dabigatran or anti-factor Xa activity on factor Xa inhibitors). If the patient does not have evidence of a therapeutic anticoagulation effect (e.g. INR < 2.0 on warfarin; or no NOAC anticoagulant effect detected), systemic thrombolysis may be considered if no access to primary PCI.

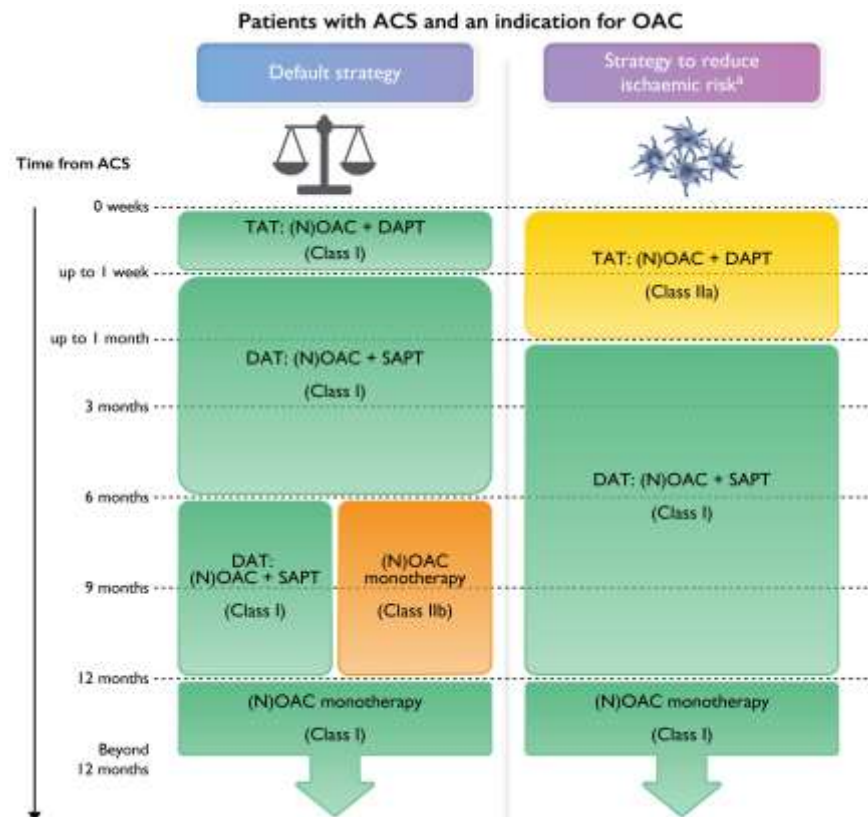


Figure 9-5: Antithrombotic regimens in patients with ACS and an indication for oral anticoagulation. OAC: preference for a NOAC over VKA for the default strategy and in all other scenarios if no contraindications. For both TAT and DAT regimens, the recommended doses for the NOACs are as follows: Apixaban 5 mg b.i.d., Dabigatran 110 mg or 150 mg b.i.d., Edoxaban 60 mg o.d., Rivaroxaban 15 mg or 20 mg o.d. NOAC dose reductions are recommended in patients based on certain criteria for each of the NOACs (including renal function, body weight, concomitant medications and age). SAPT: preference for a P2Y12 receptor inhibitor (usually clopidogrel) over aspirin. **Source:** 2023 ESC guidelines for management of acute coronary syndromes.

Table 9-5: ESC Recommendations on combining antiplatelets and OAC:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>As the default strategy for patients with AF and CHA2DS2-VASc score ≥ 1 in men and ≥ 2 in women, after up to 1 week of triple antithrombotic therapy following the ACS event, dual antithrombotic therapy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel) for up to 12 months is recommended.</i> | I | A |
| <i>During PCI, a UFH bolus is recommended in any of the following circumstances:</i> <ul style="list-style-type: none"> - <i>if the patient is on a NOAC</i> - <i>if the INR is < 2.5 in VKA-treated patients.</i> | I | C |
| <i>In patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, careful regulation of the dose intensity of VKA with a target INR of 2.0–2.5 and a time in the therapeutic range $> 70\%$ should be considered.</i> | IIa | B |
| <i>When rivaroxaban is used and concerns about HBR prevail over ischemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant SAPT or DAPT.</i> | IIa | B |
| <i>In patients at HBR, dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant SAPT or DAPT, to mitigate bleeding risk.</i> | IIa | B |
| <i>In patients requiring anticoagulation and treated medically, a single antiplatelet agent in addition to an OAC should be considered for up to 1 year.</i> | IIa | B |
| <i>In patients treated with an OAC, aspirin plus clopidogrel for longer than 1 week and up to 1 month should be considered in those with high ischemic risk or with other anatomical/procedural characteristics that are judged to outweigh the bleeding risk.</i> | IIa | C |

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| <i>In patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered.</i> | IIb | B |
| <i>The use of ticagrelor or prasugrel as part of triple antithrombotic therapy is not recommended.</i> | III | C |

Table 9-6: Suggested strategies to reduce bleeding risk related to PCI:

- *Anticoagulant doses adjusted to body weight and renal function, especially in women and older patients.*
- *Radial artery approach as default vascular access*
- *Proton pump inhibitors in patients on DAPT at higher-than-average risk of GI bleeds (i.e. history of GI ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use), or two or more of:*
 - A. *Age ≥ 65 years*
 - B. *Dyspepsia*
 - C. *Gastro-oesophageal reflux disease*
 - D. *Helicobacter pylori infection*
 - E. *Chronic alcohol use*
- **In patients on OAC:**
 - A. *PCI performed without interruption of VKAs or NOACs*
 - B. *In patients on VKAs, do not administer UFH if INR > 2.5*
 - C. *In patients on NOACs, regardless of the timing of the last administration of NOACs, add low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. **or** UFH 60 IU/kg)*
- *Aspirin is indicated but avoid pre-treatment with P2Y12 receptor inhibitors.*
- *GP IIb/IIIa inhibitors only for bailout or periprocedural complications*

Antithrombotic therapy in Chronic Coronary Syndrome

- Platelet activation and aggregation is the driver for symptomatic coronary thrombosis, forming the basis for the use of antiplatelet drugs in patients with CCS in view of a favourable balance between the prevention of ischemic events and increased risk of bleeding.
- DAPT with aspirin and an oral P2Y12 inhibitor is the mainstay of antithrombotic therapy after MI and/or PCI.
- In patients with chronic coronary syndromes undergoing PCI, clopidogrel remains the preferred P2Y12 inhibitor in addition to ASA. Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) **or** if DAPT cannot be used because of ASA intolerance (IIbC).
- The optimal timing of initiation of P2Y12 inhibition before coronary angiography and possible PCI in patients with CCS is uncertain, but increasing use of a radial artery approach and clinical experience has allowed consideration of clopidogrel pre-treatment in patients who have a high chance of requiring PCI.
- **Duration of DAPT:** After PCI for stable angina, 6 months of DAPT achieves the optimum balance of efficacy and safety in most patients. Premature discontinuation of a P2Y12 inhibitor is associated with an increased risk of stent thrombosis and is discouraged. However, a shorter duration of DAPT may be considered in those at high risk of life-threatening bleeding in view of the very low risk of stent thrombosis after 1-3 months.

| Table 9-7: ESC Recommendations for Antithrombotic in CCS: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Antithrombotic therapy in patients with CCS and in sinus rhythm: | | |
| <i>Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization.</i> | I | A |
| <i>Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.</i> | I | B |

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| <i>Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischemic stroke or transient ischemic attack.</i> | IIb | B |
| <i>Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.</i> | IIb | C |
| <i>Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischemic events and without high bleeding risk.</i> | IIa | A |
| <i>Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk.</i> | IIb | A |
| Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm: | | |
| <i>Aspirin 75-100 mg daily is recommended following stenting.</i> | I | A |
| <i>Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or > 5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1-3 months) is indicated due to risk or the occurrence of life-threatening bleeding.</i> | I | A |
| <i>Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or > 5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.</i> | IIa | A |
| <i>Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or > 5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.</i> | IIb | C |

Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance.

IIb

C

Dual pathway inhibition (DPI)

Low dose Rivaroxaban + Antiplatelet agent

- In patients with chronic vascular disease who were receiving high rates of contemporary CV therapies, such as statins and ACEIs, the risk of MACE at 1 year remained at about 3%. Therefore, novel strategies that prevent clinical events via mechanisms that extend beyond platelet inhibition are needed.
- The classic DAPT combination of aspirin and a P2Y12 inhibitor targets two pathways of platelet activation (ADP-receptor blockade with P2Y12 inhibitors and COX1 inhibition with aspirin), but platelet activation can still occur through other platelet receptors (e.g., PAR1 and PAR4).
- DPI involves the simultaneous blockade of two pathways of thrombus formation to gain synergistic benefits. DPI differs from DAPT in that it combines an anticoagulant with a single antiplatelet agent rather than combining two antiplatelet agents.
- Factor Xa and thrombin are critical for platelet activation and fibrin formation because they function as both platelet agonists and critical components of the coagulation cascade. In addition, factor Xa, through activation of PAR1 and PAR2, and thrombin, through activation of PAR1, promote pro-inflammatory cytokine production, expression of cell-adhesion molecules on endothelial cells and proliferation of endothelial cells and vascular smooth muscle cells. Therefore, reducing the concentration of thrombin with the use of an anticoagulant has been proposed as a mechanism to inhibit clot formation through both direct anticoagulant effects and indirect antiplatelet effects. Inhibition of factor Xa has also been proposed as a mechanism to modulate atherothrombosis in light of its direct effects on PAR1 and PAR2 signalling.

Switching between oral P2Y₁₂ inhibitors

Table 9-8: ESC Recommendations for Switching between oral P2Y₁₂ inhibitors:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist.</i> | I | B |
| <i>Additional switching between oral P2Y₁₂ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.</i> | IIb | C |

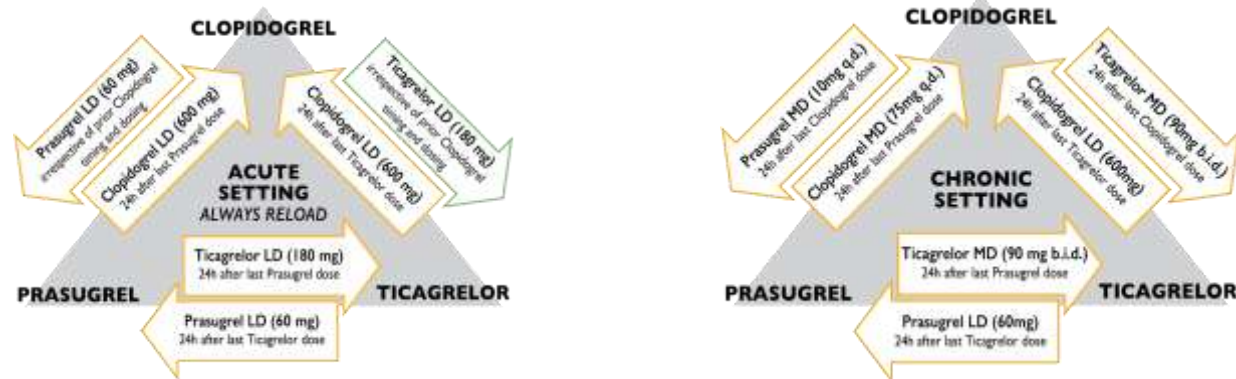


Figure 9-6: Algorithm for switching between oral P2Y₁₂ inhibitors in the acute and chronic setting. LD = loading dose; MD= maintenance dose. Acute setting is considered as a switching occurring during hospitalization. **Source:** 2017 ESC/EACTS focused update on dual antiplatelet therapy in coronary artery disease.

Antiplatelet management in non-cardiac surgery

- The management of antiplatelet therapy in patients who have undergone recent PCI and are scheduled for NCS should balance the risk of life-threatening surgical bleeding on antiplatelet therapy against the risk of life-threatening stent thrombosis due to premature DAPT discontinuation.
- Although generally not recommended, bridging with i.v. compounds (Eptifibatide/tirofiban or cangrelor) might be applicable in rare cases when DAPT cannot be interrupted before NCS.

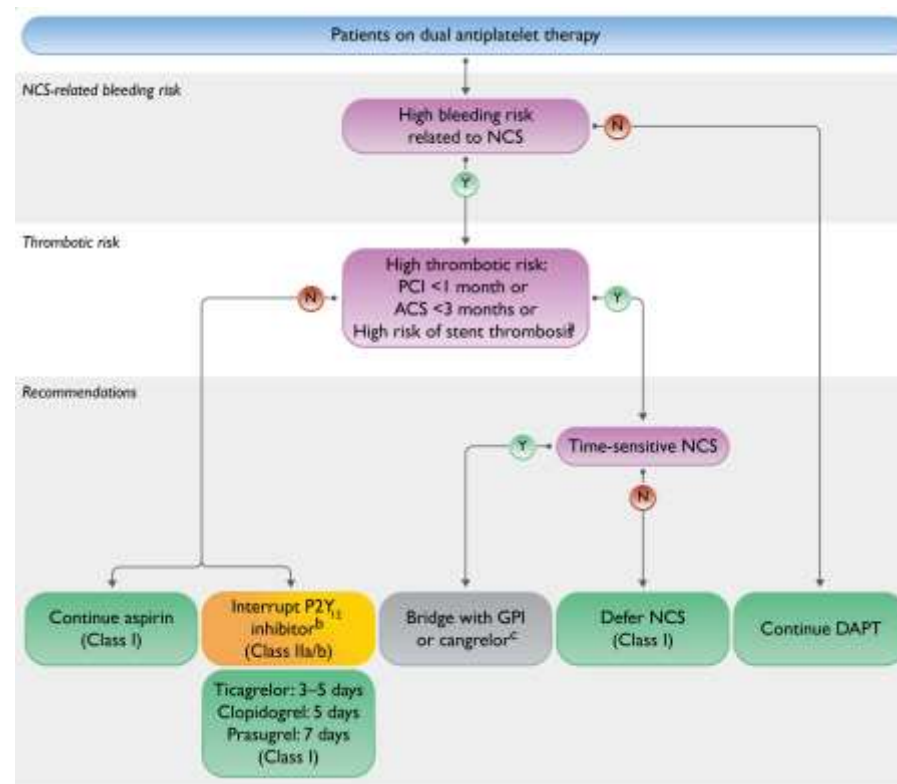


Figure 9-7: Recommendations for management of antiplatelet therapy in patients undergoing non-cardiac surgery. **(A)** defined by at least one of the following: history of stent thrombosis under antiplatelet therapy, reduced LVEF (< 40%), poorly controlled diabetes, severely impaired renal function/haemodialysis, recent complex PCI (i.e. severely calcified lesion, left main PCI, chronic total occlusion, bifurcational/crush technique, bypass graft PCI), or stent malapposition/residual dissection. **(B)** Timing of resumption after interdisciplinary risk assessment as soon as possible (within 48 h) after surgery. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

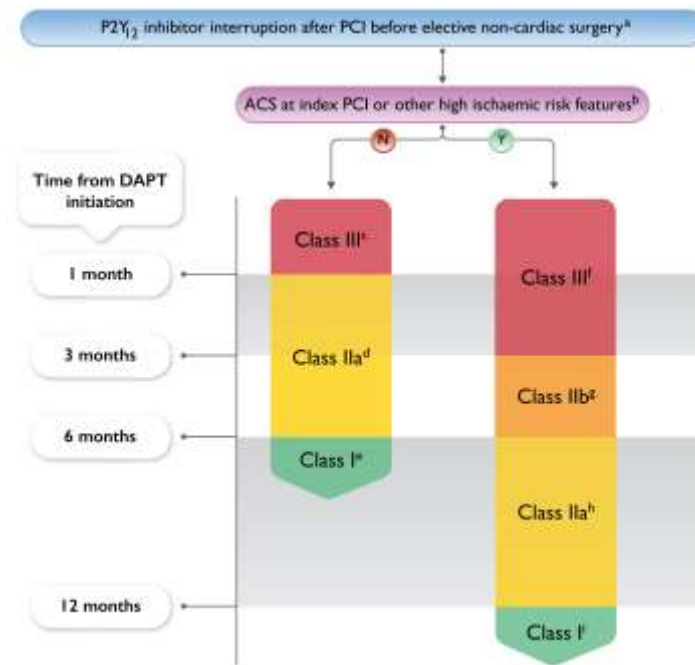


Figure 9-8: P2Y₁₂ inhibitor interruption after PCI before elective non-cardiac surgery. (A) Availability of 24 h cath-lab service is suggested in case of major surgery within 6 months in non-ACS/non-high-risk patients and within 12 months in ACS/high-risk patients. **(B) High risk of peri-operative stent thrombosis** defined by at least one of the following: history of recurrent MI, history of stent thrombosis under antiplatelet therapy, reduced LVEF (< 40%), poorly controlled diabetes, severely impaired renal function/haemodialysis, recent complex PCI (i.e. severely calcified lesion, left main PCI, chronic total occlusion, bifurcational/crush technique, bypass graft PCI), stent malapposition/residual dissection. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

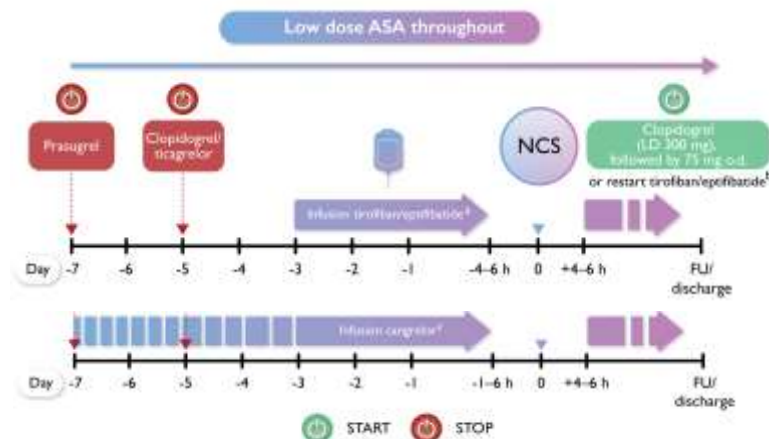


Figure 9-9: Bridging with intravenous antiplatelet agents. (A) Tirofiban: 0.1 µg/kg/min; if Cr. Cl. < 50 mL/min, adjust to 0.05 µg/kg/min. **Eptifibatide:** 2.0 µg/kg/min; if Cr. Cl. is < 50 mL/min, adjust to 1.0 µg/kg/min. **(B)** Until oral P2Y12 inhibitor therapy is possible. **(C)** Initiate within 72 h from P2Y12 inhibitor discontinuation at a dose of 0.75 µg/kg/min for a minimum of 48 h and a maximum of 7 days. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

Table 9-9: ESC Recommendations for use of antiplatelet therapy in patients undergoing noncardiac surgery:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Timing of surgery: | | |
| <i>It is recommended to delay elective NCS until 6 months after elective PCI and 12 months after an ACS.</i> | I | A |
| <i>After elective PCI, it is recommended to delay time-sensitive NCS until a minimum of 1 month of DAPT treatment has been given.</i> | I | B |

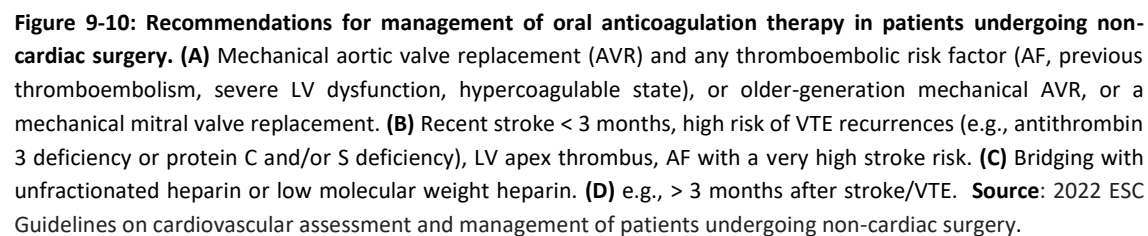
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| <i>In patients with a recent PCI scheduled for NCS, it is recommended that management of antiplatelet therapy is discussed between the surgeon, anaesthesiologist, and cardiologist.</i> | I | C |
| <i>In high-risk patients with a recent PCI (e.g., STEMI patients or high-risk NSTEMI-ACS patients), a DAPT duration of at least 3 months should be considered before time-sensitive NCS.</i> | IIa | C |
| Continuation of medication: | | |
| <i>In patients with a previous PCI, it is recommended to continue aspirin peri-operatively if the bleeding risk allows.</i> | I | B |
| Recommended time interval for drug interruption before NCS: | | |
| <i>If interruption of P2Y12 inhibitor is indicated, it is recommended to withhold ticagrelor for 3-5 days, clopidogrel for 5 days, and prasugrel for 7 days prior to NCS.</i> | I | B |
| <i>For patients undergoing high bleeding risk surgery (e.g. intracranial, spinal neurosurgery, or vitreoretinal eye surgery), it is recommended to interrupt aspirin for at least 7 days pre-operatively.</i> | I | C |
| <i>In patients without a history of PCI, interruption of aspirin at least 3 days before NCS may be considered if the bleeding risk outweighs the ischaemic risk, to reduce the risk of bleeding.</i> | IIb | B |
| Resumption of medication: | | |
| <i>If antiplatelet therapy has been interrupted before a surgical procedure, it is recommended to restart therapy as soon as possible (within 48 h) post-surgery, according to interdisciplinary risk assessment.</i> | I | C |

Anticoagulation management in non-cardiac surgery

Peri-operative management of oral anticoagulant therapy depends on surgery- and patient-related factors and the specific OAC agent (VKA or NOAC).

Surgery-related factors include urgency of the intervention and the procedure-related bleeding risk (reflecting both the risk of bleeding occurrence and the risk of adverse outcome if bleeding occurs).

Procedures where mechanical compression is unfeasible carry a high risk of serious bleeding.



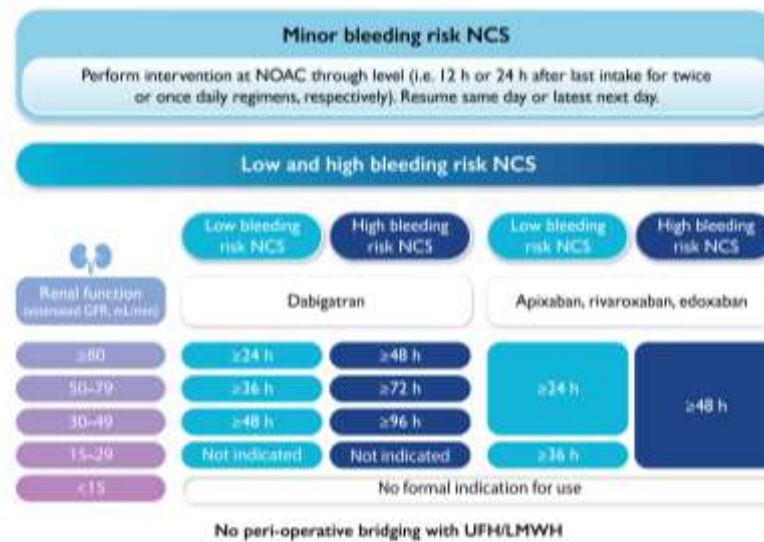


Figure 9-11: Timing of last NOAC dose before elective NCS according to renal function. Source: 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

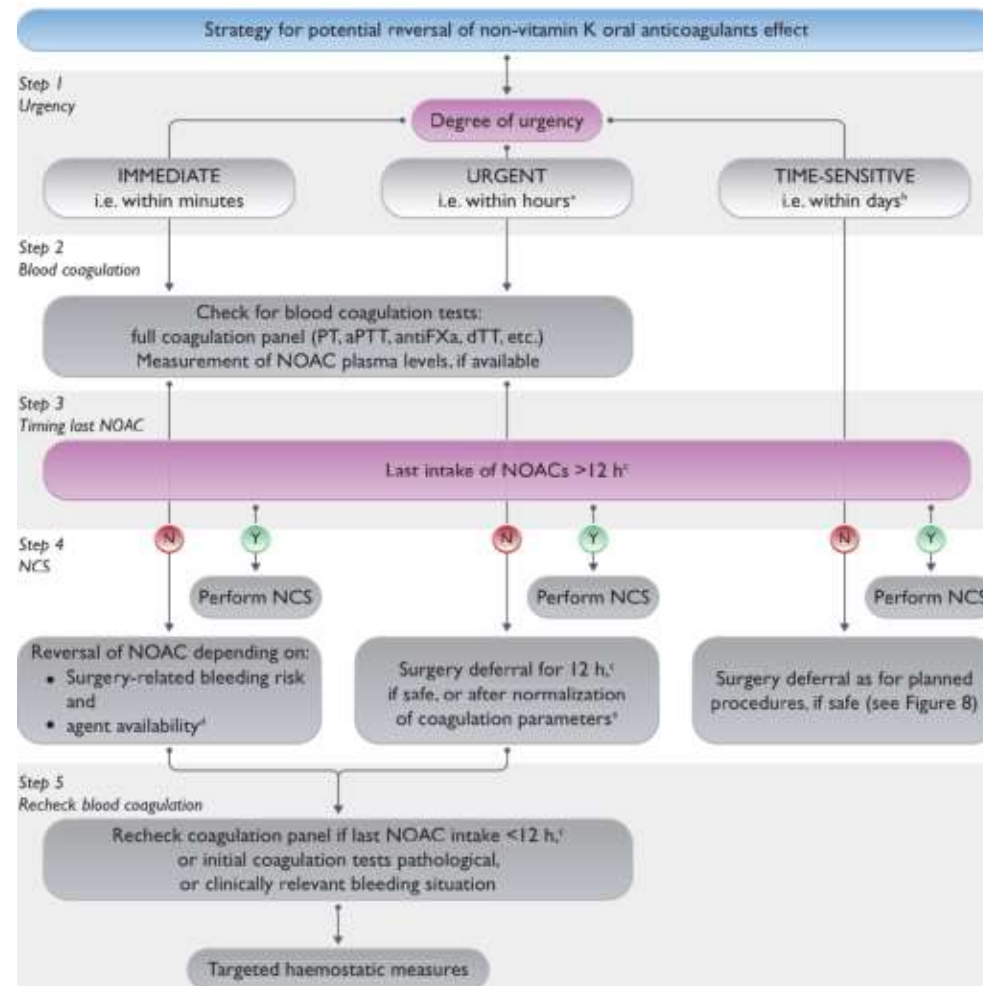


Figure 9-12: Suggested strategy for potential reversal of NOACs effect. (A) Conditions that are potentially life-threatening or that may threaten the survival of limb or organ. (B) Conditions that can be managed and procedure delayed for several days. (C) > 24 h in case of significantly reduced renal function (i.e. eGFR < 50 mL/min). (D) If specific reversal agent is unavailable, consider non-specific haemostatic agents (prothrombin complex concentrate [PCC] or activated PCC [aPCCs]). Idarucizumab has only been tested in patients undergoing urgent surgery. Andexanet has not been tested in patients requiring urgent surgery. Andexanet binds all FXa inhibitors (including UFH) nonspecifically. (E) Upon re-check. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

Table 9-10: ESC Recommendations for interruption and resumption of anticoagulants in patients undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Interruption of anticoagulation: | | |
| <i>When an urgent surgical intervention is required, it is recommended that NOAC therapy is immediately interrupted.</i> | I | C |
| <i>Idarucizumab should be considered in patients on dabigatran and requiring urgent surgical intervention with intermediate to high bleeding risk.</i> | Ila | B |
| <i>In non-minor bleeding risk procedures in patients using a NOAC, it is recommended to use an interruption regimen based on the NOAC compound, renal function, and bleeding risk.</i> | I | B |
| <i>For interventions with a very high risk of bleeding, such as spinal or epidural anaesthesia, interruption of NOACs for up to five half-lives and re-initiation after 24 h should be considered.</i> | Ila | C |
| <i>When specific reversal agents are unavailable, PCC or activated PCC should be considered for reversing NOAC effects.</i> | Ila | C |
| <i>If an urgent surgical intervention is required, specific coagulation tests and assessment of NOAC plasma levels should be considered to interpret routine coagulation tests and waning of anticoagulant effect.</i> | Ila | C |
| Continuation of medication: | | |
| <i>In minor bleeding risk surgery and other procedures where bleeding can be easily controlled, it is recommended to perform surgery without interruption of OAC therapy.</i> | I | B |
| <i>In patients using NOACs, it is recommended that minor bleeding risk procedures are performed at trough levels (typically 12-24 h after last intake).</i> | I | C |
| <i>LMWH is recommended, as an alternative to UFH, for bridging in patients with mechanical heart valves and high surgical risk.</i> | I | B |

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| <i>For patients with mechanical prosthetic heart valves undergoing NCS, bridging with UFH or LMWH should be considered if OAC interruption is needed and patients have: (i) mechanical AVR and any thromboembolic risk factor; (ii) old-generation mechanical AVR; or (iii) mechanical mitral or tricuspid valve replacement.</i> | IIa | C |
| <i>Bridging of OAC therapy is not recommended in patients with low/moderate thrombotic risk undergoing NCS.</i> | III | B |
| Start/resumption of medication: | | |
| <i>If bleeding risk with resumption of full-dose anticoagulation outweighs the risk of thromboembolic events, postponing therapeutic anticoagulation 48-72 h after the procedure may be considered, using post-operative thromboprophylaxis until resumption of full OAC dose is deemed safe.</i> | IIb | C |
| <i>Use of reduced-dose NOAC to attenuate the risk of post-operative bleeding is not recommended.</i> | III | C |

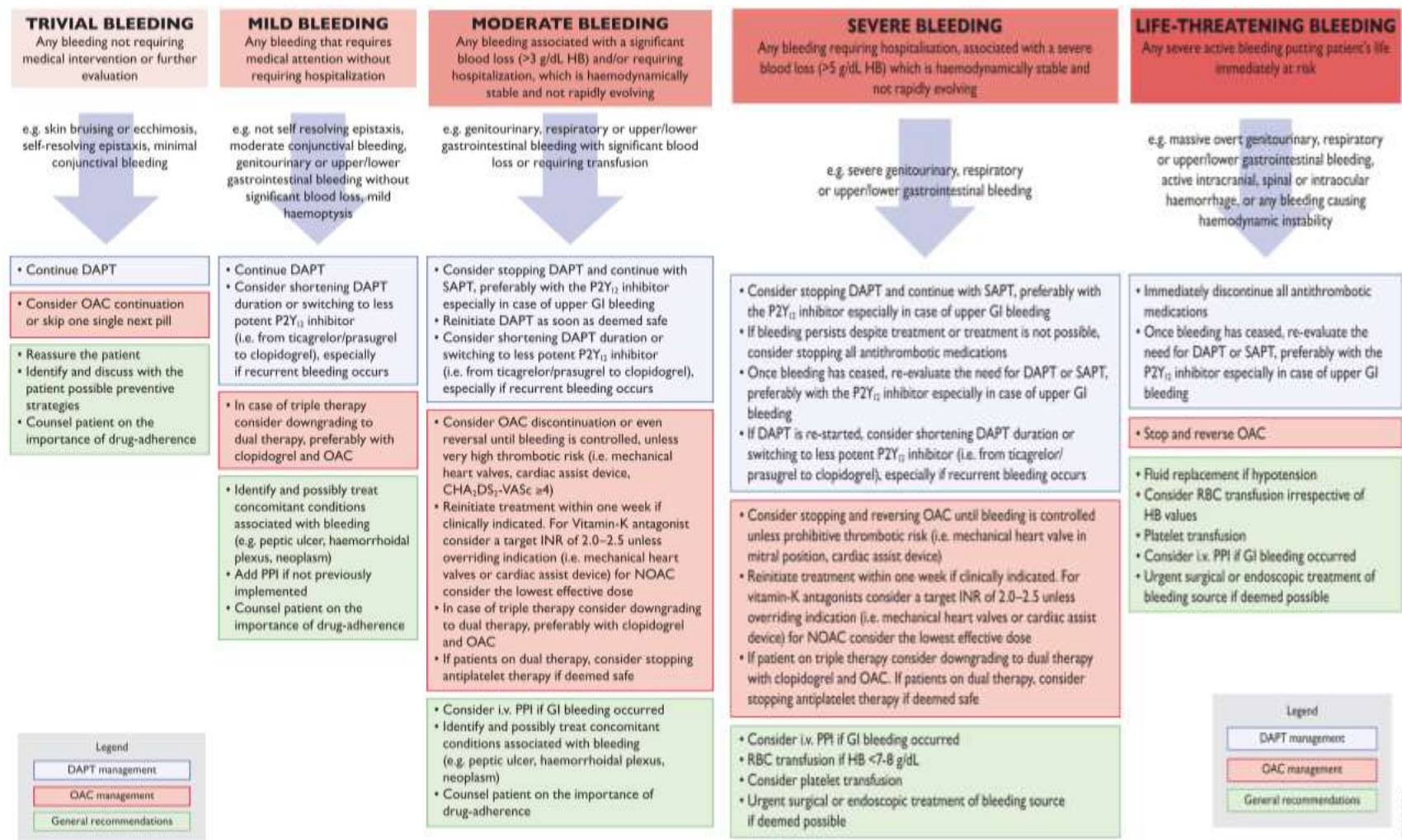


Figure 9-13: Practical recommendations for the management of bleeding in patients treated with dual antiplatelet therapy with or without concomitant oral anticoagulation. Blue boxes refer to management of antiplatelet therapy. Dark-red boxes refer to the management of oral anticoagulation. Light-green boxes refer to general recommendation for patients' safety.
Source: 2017 ESC/EACTS focused update on dual antiplatelet therapy in coronary artery disease.

Important trials about use of Antithrombotics in IHD:

| Table 9-11: Clinical trials of use of Antithrombotics in IHD: | |
|---|---|
| Trial (date) | Summary |
| Antiplatelet in ACS: | |
| CURE (2001) | <p>Aim: To assess the safety and efficacy of clopidogrel, on the background of aspirin therapy, in the management of patients with NSTEMI-ACS</p> <p>Study: 12,562 patients who had presented within 24 hours after the onset of symptoms were randomly assigned to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo in addition to aspirin for 3 to 12 months. The antiplatelet agent clopidogrel has beneficial effects in patients with NSTEMI-ACS. However, the risk of major bleeding is increased among patients treated with clopidogrel.</p> |
| CURRENT-OASIS-7 (2010) | <p>Aim: To compare the efficacy and safety of a high or low daily dose of aspirin, and standard-dose compared with double-dose clopidogrel, among patients with ACS.</p> <p>Study: 25,086 patients with ACS who were referred for an invasive strategy were randomly assigned to either double-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and either higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily). The primary outcome was CV death, MI, or stroke at 30 days. There was no significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to CV death, MI, or stroke.</p> |
| PEGASUS-TIMI 54 (2015) | <p>Aim: To assess the efficacy and safety of ticagrelor after an ACS.</p> <p>Study: 21,162 patients who had MI 1 to 3 years earlier were randomly assigned to ticagrelor (90 mg twice daily), ticagrelor (60 mg twice daily), or placebo. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. All the patients were to receive low-dose aspirin and</p> |

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| | <i>were followed for a median of 33 months. Ticagrelor (the two doses) significantly reduced the risk of CV death, MI, or stroke and increased the risk of major bleeding.</i> |
| ATLANTIC (2014) | <p>Aim: <i>To assess whether prehospital administration of ticagrelor can improve coronary reperfusion and the clinical outcome.</i></p> <p>Study: <i>1862 patients with ongoing STEMI of < 6 hours' duration, were randomized to prehospital (in the ambulance) versus in-hospital (in the catheterization laboratory) treatment with ticagrelor. The coprimary endpoints were the proportion of patients who did not have a 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients who did not have TIMI flow grade 3 in the IRA at initial angiography. Prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion.</i></p> |
| ACCOAST (2013) | <p>Aim: <i>To study if pretreatment with prasugrel in all patients would be superior to prasugrel given post-angiography in patients undergoing PCI.</i></p> <p>Study: <i>4033 patients with NSTEMI who were scheduled to undergo coronary angiography within 2 to 48 hours were randomly assigned to receive prasugrel (a 30-mg loading dose) before the angiography (pretreatment group) or placebo (control group). When PCI was indicated, an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI and 60 mg of prasugrel was given in the control group. Pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding.</i></p> |
| Duration of DAPT: | |
| DAPT (2014) | <p>Aim: <i>To investigate if prolonged DAPT duration (30 months) was superior to 12 months in patients undergoing DES and BMS PCI.</i></p> <p>Study: <i>9961 patients were enrolled after they had undergone a coronary stent procedure in which DES was placed. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients</i></p> |

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| | <p>were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months; all patients continued receiving aspirin. DAPT beyond 1 year after placement of a DES, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and MACE and cerebrovascular events but was associated with an increased risk of bleeding.</p> |
| RESET (2012) | <p>Aim: To evaluate treatment with a zotarolimus-eluting stent and 3 months of DAPT compared with other DES and 12 months of DAPT.</p> <p>Study: 2,117 patients with coronary artery stenosis were randomly assigned into 2 groups according to DAPT duration and stent type: 3-month DAPT following zotarolimus-eluting stent (E-ZES) implantation (E-ZES + 3-month DAPT) versus 12-month DAPT following the other DES implantation (standard therapy). E-ZES + 3-month DAPT was noninferior to the standard therapy with respect to the occurrence of the primary endpoint.</p> |
| SMART-DATE (2018) | <p>Aim: To assess whether a 6-month duration would be non-inferior to the 12-month or longer duration of DAPT in ACS undergoing PCI.</p> <p>Study: 2712 patients with ACS undergoing PCI were randomly assigned to either the 6-month DAPT group or to the 12-month or longer DAPT group, with stratification by site, clinical presentation, and diabetes. Prolonged DAPT in patients with ACS without excessive risk of bleeding should remain the standard of care.</p> |
| SMART-CHOICE (2019) | <p>Aim: To compare the safety and efficacy of short-duration (3 months) with longer duration DAPT (12 months) in patients undergoing PCI.</p> <p>Study: 2,993 eligible patients were randomized to either DAPT for 3 months or 12 months. In the former group, after 3 months, aspirin was discontinued and P2Y12 inhibitor monotherapy was continued. Eligible patients were randomized to either DAPT for 3 months or 12 months. Stratification was performed by type of DES used. Short-duration DAPT (3 months) is noninferior to longer-duration DAPT (12 months) among unselected patients undergoing PCI with a DES.</p> |
| STOPDAPT-2 (2019) | <p>Aim: To evaluate 1-month DAPT compared with 12-month DAPT among patients undergoing PCI.</p> |

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| | <p>Study: 3,045 patients undergoing PCI were randomized to 1 month of DAPT followed by clopidogrel monotherapy for 5 years versus 12 months of DAPT followed by aspirin monotherapy for 5 years. 1 month of DAPT followed by clopidogrel monotherapy was noninferior to 12 months of DAPT followed by aspirin monotherapy at preventing net adverse clinical events.</p> |
| GLOBAL LEADERS (2018) | <p>Aim: To evaluate 1 month of aspirin plus ticagrelor followed by 23 months of ticagrelor monotherapy compared with 1 year of DAPT (aspirin plus either clopidogrel or ticagrelor) followed by 1 year of aspirin monotherapy among patients undergoing PCI with a biolimus-eluting stent.</p> <p>Study: 15,968 patients undergoing PCI for stable or unstable coronary disease were randomized to DAPT aspirin/ticagrelor for 1 month, followed by ticagrelor for 23 months versus DAPT for 12 months (aspirin/clopidogrel for stable coronary disease or aspirin/ticagrelor for unstable coronary disease), followed by aspirin for 12 months. Among patients who underwent PCI with a biolimus-eluting stent, 1 month of DAPT followed by ticagrelor monotherapy for 23 months was noninferior, but not superior to 12 months of DAPT followed by aspirin monotherapy for 12 months. The composite outcome, components of the primary outcome, and major bleeding were similar between treatment groups.</p> |
| TROPICAL-ACS (2017) | <p>Aim: To evaluate de-escalation of antiplatelet therapy compared with control among patients who received a coronary stent for ACS.</p> <p>Study: 2,610 patients with ACS who underwent PCI were randomized to de-escalation of antiplatelet therapy vs. prasugrel for 12 months. In the de-escalation group, participants were treated with prasugrel for 1 week, then clopidogrel for 1 week at which time they underwent platelet function testing. De-escalation of maintenance antiplatelet therapy was noninferior to 12 months of prasugrel. De-escalation of antiplatelet therapy was guided by platelet function testing. This strategy was associated with noninferiority regarding the primary outcome of CV death, MI, stroke, or bleeding BARC ≥ 2. Younger patients possibly experienced a greater net clinical benefit (due to less bleeding) compared with older patients with de-escalation of antiplatelet therapy.</p> |

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| TWILIGHT (2019) | <p>Aim: <i>To compare the safety and efficacy of a short-duration DAPT (3 months) followed by ticagrelor monotherapy compared with longer duration DAPT (12 months) among patients undergoing PCI with a DES and with ≥ 1 high risk feature of ischemia or bleeding.</i></p> <p>Study: <i>9006 patients who were at high risk for bleeding or an ischemic event and had undergone PCI were randomly assigned to ticagrelor alone and to ticagrelor plus aspirin. After 3 months of treatment with ticagrelor plus aspirin, patients who had not had a major bleeding event or ischemic event continued to take ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year. Among high-risk patients who underwent PCI and completed 3 months of DAPT, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, MI, or stroke.</i></p> |
| TICO (2020) | <p>Aim: <i>To evaluate ticagrelor monotherapy after 3 months of DAPT compared with 12 months of DAPT after PCI for ACS.</i></p> <p>Study: <i>3056 Patients undergoing PCI for ACS were randomized to ticagrelor monotherapy after 3 months of DAPT versus standard therapy. The primary outcome was net adverse clinical events (death, MI, stent thrombosis, stroke, target vessel revascularization, or TTIMI major bleeding at 12 month. Ticagrelor monotherapy after 3 months of DAPT was superior to standard therapy of DAPT for 12 months</i></p> |
| MASTER DAPT (2021) | <p>Aim: <i>To compare abbreviated antiplatelet therapy with standard antiplatelet therapy among high bleeding risk patients who underwent PCI.</i></p> <p>Study: <i>4434 patients at high bleeding risk after they had undergone implantation of a biodegradable-polymer sirolimus-eluting coronary stent were randomly assigned to discontinue DAPT after one month (abbreviated therapy) or to continue it for at least 2 additional months (standard therapy). One month of DAPT was noninferior to the continuation of therapy for at least 2 additional months with regard to the occurrence of net adverse clinical events and major adverse cardiac or cerebral events; abbreviated therapy also resulted in a lower incidence of major or clinically relevant non major bleeding.</i></p> |
| Comparison between the antiplatelet agents: | |

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| ISAR-REACT 5 RCT (2019) | <p>Aim: To evaluate ticagrelor compared with prasugrel among patients with an ACS undergoing planned coronary angiography.</p> <p>Study: 4018 patients who presented with ACS and for whom invasive evaluation was planned were randomly assigned to receive either ticagrelor or prasugrel. The primary end point was the composite of death, MI, or stroke at 1 year. The incidence of death, MI, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, with no significant difference in major bleeding.</p> |
| PLATO (2009) | <p>Aim: To determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in patients with ACS.</p> <p>Study: 18,624 patients admitted to the hospital with ACS were randomly assigned to ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of CV events. Ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, MI, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.</p> |
| TRITON-TIMI-38 (2007) | <p>Aim: To evaluate treatment with prasugrel compared with clopidogrel among patients undergoing planned PCI for ACS.</p> <p>Study: 13,608 patients with moderate-to-high-risk ACS with scheduled PCI were randomly assigned to receive prasugrel (a 60-mg loading dose and a 10-mg daily thereafter) or clopidogrel (a 300-mg loading dose and a 75-mg daily thereafter), for 6 to 15 months. The primary efficacy end point was CV mortality, nonfatal MI, or nonfatal stroke. The key safety end point was major bleeding. Prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups.</p> |
| TREAT (2019) | <p>Aim: To evaluate ticagrelor compared with clopidogrel among patients who received fibrinolytic therapy for STEMI.</p> |

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| | <p>Study: 3,799 patients (age < 75 years) with STEMI receiving fibrinolytic therapy were randomized to ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300- to 600-mg loading dose, 75 mg daily thereafter). The primary outcome was TIMI major bleeding. Among patients <75 years of age who were treated with fibrinolysis for STEMI, delayed administration of ticagrelor was noninferior to clopidogrel. There was no excess of major bleeding, fatal bleeding, or intracranial bleeding with ticagrelor vs. clopidogrel.</p> |
| TRILOGY-ACS (2012) | <p>Aim: To compare between prasugrel and clopidogrel in patients with NSTEMI-ACS for medical management without revascularization.</p> <p>Study: 7243 patients with NSTEMI-ACS for medical management without revascularization were evaluated up to 30 months of treatment with prasugrel (10 mg daily if age < 75 years and 5 mg if < 75 yrs) versus clopidogrel (75 mg daily). Among patients with NSTEMI-ACS, prasugrel did not significantly reduce the frequency of the primary end point, as compared with clopidogrel, and similar risks of bleeding were observed.</p> |
| CHAMPION PHOENIX (2013) | <p>Aim: To evaluate treatment with the i.v cangrelor compared with the oral clopidogrel among patients undergoing PCI.</p> <p>Study: 11,145 patients who were undergoing urgent or elective PCI and receiving guideline-recommended therapy were randomly assigned to receive a bolus and infusion of cangrelor or to receive a loading dose of 600 mg or 300 mg of clopidogrel. Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding.</p> |
| POPular Genetics (2019) | <p>Aim: To determine whether a CYP2C19genotype–guided strategy for selection of oral P2Y₁₂inhibitors can reduce bleeding risk without increasing thrombotic risk in patients with STEMI undergoing primary PCI.</p> <p>Study: 2488 patients undergoing primary PCI with stent implantation were assigned to receive either a P2Y₁₂ inhibitor on the basis of early CYP2C19 genetic testing (genotype-guided group) or standard treatment with either ticagrelor or prasugrel (standard-treatment group) for 12 months. In the genotype-guided group, carriers of CYP2C19*2 or CYP2C19*3 loss-of-function alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel. The two primary outcomes were net adverse clinical events — defined as death from any</p> |

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| | <p>cause, MI, definite stent thrombosis, stroke, or major bleeding defined according to PLATO criteria — at 12 month. In patients undergoing primary PCI, a CYP2C19 genotype–guided strategy for selection of oral P2Y₁₂ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding.</p> |
| TOPIC (2017) | <p>Aim: To evaluate the benefit of switching DAPT from aspirin plus a newer P2Y₁₂ blocker to aspirin plus clopidogrel 1 month after ACS.</p> <p>Study: 645 patients admitted with ACS requiring coronary intervention, on aspirin and a newer P2Y₁₂ blocker (prasugrel and ticagrelor) and without adverse event at 1 month, were assigned to switch to aspirin and clopidogrel (switched DAPT) or continuation of their drug regimen (unchanged DAPT). The primary outcome was a composite of CV death, urgent revascularization, stroke and bleeding as defined by BARC classification ≥ 2 at 1 year post ACS. A switched DAPT is superior to an unchanged DAPT strategy to prevent bleeding complications without increase in ischaemic events following ACS.</p> |
| TALOS-AMI (2021) | <p>Aim: To assess the safety and efficacy of uniform unguided de-escalation strategy of DAPT from ticagrelor to clopidogrel after acute MI</p> <p>Study: 2697 patients with acute MI receiving aspirin and ticagrelor without major ischaemic or bleeding events during the first month after index PCI were randomly assigned to a de-escalation (clopidogrel plus aspirin) or active control (ticagrelor plus aspirin) group. Unguided de-escalation without a loading dose of clopidogrel was adopted when switching from ticagrelor to clopidogrel. The primary endpoint was a composite of CV death, MI, stroke, or bleeding type 2, 3, or 5 according to BARC criteria from 1 to 12 months. A non-inferiority test was done to assess the safety and efficacy of de-escalation DAPT compared with standard treatment. In stabilised patients with acute MI after index PCI, a uniform unguided de-escalation strategy significantly reduced the risk of net clinical events up to 12 months, mainly by reducing the bleeding events.</p> |

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| HOST-REDUCE-POLYTECH-ACS (2022) | <p>Aim: <i>To assess whether prasugrel dose de-escalation therapy feasible for patients after ACS in complex PCI.</i></p> <p>Study: <i>2024 patients with ACS who were receiving PCI were randomized to a prasugrel dose de-escalation (5 mg daily) at 1 month post-PCI group or a conventional (10 mg daily) group. Complex PCI was defined as having at least 1 of the following features: 3 or more stents implanted, 3 or more lesions treated, bifurcation PCI, total stent length 60 mm or larger, left main PCI, or heavy calcification. The primary end points were MACE (major adverse cardiac event, a composite of cardiovascular death, nonfatal myocardial infarction, stent thrombosis, and repeat revascularization) at 1 year for ischemic outcomes, and BARC class 2 or higher bleeding events at 1 year for bleeding outcomes. prasugrel dose de-escalation compared with conventional therapy was not associated with an increased risk of ischemic outcomes but may reduce the risk of minor bleeding events at 1 year, irrespective of PCI complexity.</i></p> |
| Anticoagulation in CCS: | |
| COMPASS (2017) | <p>Aim: <i>To evaluate anticoagulation strategies with rivaroxaban among patients with stable atherosclerosis.</i></p> <p>Study: <i>27,395 participants with stable atherosclerotic vascular disease were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of CV death, stroke, or MI. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months. Those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better CV outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better CV outcomes than aspirin alone and resulted in more major bleeding events.</i></p> |
| Anticoagulation in ACS: | |
| MATRIX (2015) | <p>Aim: <i>To assess whether bivalirudin is superior to unfractionated heparin and discretionary use of glycoprotein IIb/IIIa inhibitors.</i></p> |

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| | <p>Study: 7213 patients with an ACS for whom PCI was anticipated to receive either bivalirudin or unfractionated heparin. Patients in the bivalirudin group were subsequently randomly assigned to receive or not to receive a post-PCI bivalirudin infusion. Primary outcomes for the comparison between bivalirudin and heparin were the occurrence of MACE (a composite of death, MI, or stroke) and net adverse clinical events (a composite of major bleeding or MACE). The rates of MACE and net adverse clinical events were not significantly lower with bivalirudin than with unfractionated heparin. The rate of the composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events was not significantly lower with a post-PCI bivalirudin infusion than with no post-PCI infusion.</p> |
| Anticoagulation in STEMI: | |
| OASIS-6 (2006) | <p>Aim: To evaluate the effect of fondaparinux when initiated early and given for up to 8 days vs usual care in patients with STEMI.</p> <p>Study: 12,092 patients with STEMI were randomly assigned to fondaparinux 2.5 mg once daily or usual care (placebo in those in whom UFH is not indicated [stratum 1] or UFH for up to 48 hours followed by placebo for up to 8 days [stratum 2]) for up to 8 days. From day 3 through day 9, all patients received either fondaparinux or placebo according to the original randomized assignment. In patients with STEMI, particularly those not undergoing primary PCI, fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes.</p> |
| HORIZONS-AMI (2008) | <p>Aim: To examine the safety and efficacy of bivalirudin monotherapy compared with UFH plus routine GPIs in patients undergoing primary PCI.</p> <p>Study: 3602 patients undergoing planned primary PCI for acute STEMI were randomized to treatment during PCI with bivalirudin or heparin plus GP IIb/IIIa inhibitor. Anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events.</p> |
| HEAT-PPCI | <p>Aim: To evaluate bivalirudin compared with UFH among patients undergoing primary PCI.</p> |

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| (2014) | <p>Study: 1812 patients undergoing emergency angiography were randomly assigned to to heparin (70 U/kg) or bivalirudin (bolus 0.75 mg/kg; infusion 1.75 mg/kg per h). Compared with bivalirudin, heparin reduces the incidence of major adverse ischaemic events in the setting of PPCI, with no increase in bleeding complications. Systematic use of heparin rather than bivalirudin would reduce drug costs substantially.</p> |
| <p>BRIGHT-4 (2022)</p> | <p>Aim: To evaluate the safety and efficacy of a high-dose infusion of bivalirudin after primary PCI compared with unfractionated heparin (UFH).</p> <p>Study: 6016 patients presented with STEMI within 48 hours undergoing primary PCI were randomized in an open-label 1:1 fashion to either bivalirudin or UFH. The primary outcome, all-cause bleeding or BARC 3-5 bleeding at 30 days. bivalirudin is superior to UFH monotherapy in reducing bleeding and ischemic events at 30 days among patients with STEMI undergoing primary PCI.</p> |
| <p>ATOLL (2011)</p> | <p>Aim: To evaluate treatment with enoxaparin compared with unfractionated heparin (UFH) among patients undergoing primary PCI.</p> <p>Study: 910 STEMI patients were randomized Prior to primary PCI to open-labeling i.v enoxaparin 0.5 mg/kg versus UFH 70-100 U/kg. The use of a glycoprotein inhibitor was left to operator discretion, and when used, the recommended dose of UFH was lowered to 50-70 U/kg. Primary endpoints were All-cause death, complications of MI, procedural failure, or non-CABG major bleeding. Enoxaparin did not reduce the primary outcome, although secondary ischemic outcomes were reduced, and bleeding was similar between the groups.</p> |
| <p>Anticoagulation in NSTEMI-ACS:</p> | |
| <p>ESSENCE (1997)</p> | <p>Aim: To evaluate the efficacy of enoxaparin versus unfractionated heparin, plus aspirin, in patients with rest angina or non-Q-wave infarction.</p> <p>Study: 3171 patients with angina at rest or non-Q-wave MI to receive either enoxaparin (1 mg/kg S.C BID), or continuous i.v UFH. Therapy was continued for a minimum of 48 hours to a maximum of 8 days, and we collected data on important coronary end points over a period of 30 days. Antithrombotic therapy with enoxaparin plus aspirin was more effective than UFH plus aspirin in reducing the incidence of ischemic events</p> |

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| | <i>in patients with NSTEMI-ACS in the early phase. This benefit of enoxaparin was achieved with an increase in minor but not in major bleeding.</i> |
| SYNERGY (2004) | <p>Aim: <i>To compare enoxaparin vs unfractionated heparin in patients with NSTEMI-ACS managed with an early invasive approach.</i></p> <p>Study: <i>10,027 high-risk patients with NSTEMI-ACS to be treated with an intended early invasive strategy were randomly assigned to S.C enoxaparin or i.v. UFH. Enoxaparin was not superior to UFH but was noninferior for the treatment of high-risk patients with NSTEMI-ACS. Enoxaparin is a safe and effective alternative to UFH and the advantages of convenience should be balanced with the modest excess of major bleeding.</i></p> |
| OASIS-5 (2005) | <p>Aim: <i>To evaluate treatment with fondaparinux compared with enoxaparin among patients with NSTEMI-ACS.</i></p> <p>Study: <i>20,078 patients with ACS were randomly assigned to receive either fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg twice daily) for a mean of six days and evaluated death, MI, or refractory ischemia at nine days (the primary outcome); major bleeding; and their combination. Patients were followed for up to six months. Upstream therapy with fondaparinux compared with upstream enoxaparin substantially reduces major bleeding while maintaining efficacy, resulting in superior net clinical benefit. The use of standard UFH in place of fondaparinux at the time of PCI seems to prevent angiographic complications, including catheter thrombus, without compromising the benefits of upstream fondaparinux.</i></p> |
| Patients requiring anticoagulation and antiplatelet therapy: | |
| ISAR-TRIPLE (2015) | <p>Aim: <i>To compare a 6-week versus a 6-month duration of triple therapy in patients undergoing DES implantation.</i></p> <p>Study: <i>614 patients receiving OAC who underwent DES implantation were randomized to either 6-week clopidogrel therapy or 6-month clopidogrel therapy. The primary endpoint was a composite of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding at 9 months. Six weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes. These results suggest that physicians should weigh</i></p> |

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| | <i>the trade-off between ischemic and bleeding risk when choosing the shorter or longer duration of triple therapy.</i> |
| WOEST (2013) | <p>Aim: <i>To assess the hypothesis that the combination warfarin & clopidogrel is superior to triple therapy (warfarin + clopidogrel + aspirin) with respect to bleeding complications while equally safe with respect to the prevention of thrombotic complications.</i></p> <p>Study: <i>573 patients on oral anticoagulation therapy undergoing PCI were loaded with clopidogrel (300 mg 24 hours before or 600 mg 4 hours before PCI) or received clopidogrel 75 mg daily for at least 7 days before PCI. During PCI, anticoagulation therapy was maintained where possible with a target INR of 2.0. The use of clopidogrel alone compared with aspirin plus clopidogrel reduced the frequency of all bleeding events. This was accomplished without an increase in adverse ischemic events.</i></p> |
| PIONEER AF-PCI (2016) | <p>Aim: <i>To evaluate three strategies of anticoagulation/antiplatelet therapy in patients with AF undergoing PCI.</i></p> <p>Study: <i>2124 participants with nonvalvular AF who had undergone PCI with stenting were randomly assigned to receive: (1) low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months, (2) very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, or (3) standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months.</i></p> <p><i>the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with lower clinically significant bleeding than was standard therapy with a VKA plus DAPT for 1, 6, or 12 months. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy.</i></p> |
| RE-DUAL PCI (2017) | <p>Aim: <i>To compare dual therapy with triple therapy among patients with AF undergoing coronary revascularization.</i></p> <p>Study: <i>2725 patients with AF who had undergone PCI were randomly assigned to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin for 1 to 3 months (triple-therapy group) <u>or</u> dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and</i></p> |

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| | <i>no aspirin (dual-therapy groups). The risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events.</i> |
| AUGUSTUS (2019) | <p>Aim: <i>To evaluate the role of dual therapy compared with triple therapy among patients with AF undergoing coronary revascularization.</i></p> <p>Study: <i>4614 patients with AF who had an ACS or had undergone PCI taking a P2Y12 inhibitor and apixaban or VKA were randomly assigned to receive aspirin or matching placebo for 6 months. An antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included VKA, aspirin, or both.</i></p> |
| ENTRUST AF PCI (2020) | <p>Aim: <i>To evaluate edoxaban/clopidogrel compared with vitamin K antagonist/DAPT among patients with AF who recently underwent PCI.</i></p> <p>Study: <i>1506 patients with atrial fibrillation and recent PCI were randomized to edoxaban 60 mg daily plus clopidogrel 75 mg daily for 12 months vs. VKA and clopidogrel 75 mg daily for 12 months plus aspirin (100 mg once daily, for 1-12 months). Edoxaban/clopidogrel vs. VKA/DAPT was noninferior for bleeding, with similar ischemic outcomes. The results were the same in either acute or chronic coronary disease.</i></p> |
| Dual Pathway inhibition: | |
| ATLAS-ACS 2-TIMI 51 (2012) | <p>Aim: <i>To assess the safety and efficacy of two doses of rivaroxaban in patients with recent ACS and at high risk for recurrent ischemic events.</i></p> <p>Study: <i>15,526 patients with a recent ACS were randomly assigned to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. All patients were to receive standard medical therapy, including low-dose aspirin; they were to receive a thienopyridine (either clopidogrel or ticlopidine) according to the national or local guidelines. The primary efficacy end point was a composite of death from CV causes, MI, or stroke. Rivaroxaban reduced the risk of the composite endpoint of death from CV</i></p> |

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| | <i>causes, MI, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.</i> |
| GEMINI-ACS-1 (2017) | <p>Aim: To assess rivaroxaban 2.5 mg twice daily versus aspirin 100 mg daily, in addition to clopidogrel or ticagrelor for patients with ACS.</p> <p>Study: 3037 patients with ACS were randomly assigned within 10 days after admission to receive aspirin and to receive rivaroxaban in addition to clopidogrel or ticagrelor (chosen at investigator discretion before randomisation) and continued for 6–12 months. A dual pathway antithrombotic therapy approach combining low-dose rivaroxaban with a P2Y₁₂ inhibitor for the treatment of patients with ACS had similar risk of clinically significant bleeding as aspirin and a P2Y₁₂ inhibitor.</p> |
| COMPASS (2017) | <p>Aim: To evaluate anticoagulation strategies with rivaroxaban among patients with stable atherosclerosis.</p> <p>Study: 27,395 participants with stable atherosclerotic vascular disease were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of CV death, stroke, or MI. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months. Those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better CV outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better CV outcomes than aspirin alone and resulted in more major bleeding events.</p> |
| COMMANDER-HF (2018) | <p>Aim: To assess the efficacy and safety of Rivaroxaban in reducing the risk of death, MI, or stroke in patients with HF and CAD after episode of DHF.</p> <p>Study: 5022 patients who had at least a 3-month history of chronic heart failure, LVEF ≤ 40%, and coronary artery disease and who had been treated for an episode of worsening HF within the previous 21 days were randomly assigned to receive rivaroxaban (2.5 mg twice daily) or placebo. Rivaroxaban was not associated with a significantly lower rate of death, MI, or stroke than placebo among patients with worsening chronic heart failure, reduced LVEF, coronary artery disease, and no AF.</p> |

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| VOYAGER PAD (2020) | <p>Aim: <i>To evaluate rivaroxaban/aspirin compared with placebo/aspirin in patients with lower extremity PAD undergoing revascularization.</i></p> <p>Study: <i>6564 patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. Rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone.</i></p> |
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Chapter 10:

Coronary Assessment and Intervention

Vascular Access Management

▪ Femoral Access:

- If heparin is used during PCI, the sheath is removed when Activated Clotting Time (ACT) < 170 s (~2-3 hrs after PCI).
- If bivalirudin is used, the sheath is removed 1.5 hours after the infusion is discontinued, the half-life being 25 minutes in patients with normal renal function; wait 2-3 hours in advanced renal failure (GFR < 30 ml/min), where the half-life is ~1 hour.
- If enoxaparin is used, remove the sheath 6-8 hours after the last SQ dose of enoxaparin.
- General duration of manual pressure over the femoral artery: 10 minutes if a 4 Fr sheath is used and 5 more minutes for each higher French size. 4-6 Fr sheaths are usually used for diagnostic coronary angiography; ≥ 5 Fr sheaths are used for PCI.
- In general, the patient is maintained flat in bed 4 hrs after 4 Fr sheath removal, and 6 hrs after 6 Fr sheath removal.
- A vascular closure device may be used (polyethylene glycol, collagen, or suture-based device). When a closure device is used, the sheath is pulled out immediately after PCI, even while anticoagulation with heparin or bivalirudin is therapeutic; prolonged occlusive manual compression is not needed, and the patient can ambulate 2-4 hours later. *However, while convenient, closure devices do not reduce local vascular and bleeding complications.*

▪ Radial Access:

- Heparin is given regardless of PCI to prevent radial occlusion (UFH 5000 units or 50 units/kg). If an intervention is planned, a therapeutic dose of bivalirudin may be given instead of UFH.
- The sheath is removed at the end of the procedure and hemostasis achieved with the use of an inflatable transradial band. *Patent hemostasis* should be used, meaning that the transradial band is only inflated with enough volume to stop the bleeding,

not more; and pulse oximetry should continue to show a waveform even with ulnar occlusion. The band is kept untouched for 30 min then deflated progressively (~3 ml every 15 min).

Patients are generally hospitalized for 1 day after PCI, during which they are monitored for access complications, contrast nephropathy, and periprocedural MI. Low-risk patients without major comorbidities (HF, renal failure) undergoing a non-complex PCI through a radial access may be discharged on the day of the procedure.

Balloon angioplasty

- **Mechanisms of action:** Angioplasty expands the external elastic membrane (EEM) of the stenotic segment, creating a larger total vessel area that compensates for the intimal plaque; this is similar to the positive remodeling phenomenon.
- **Pitfalls:**
 - **Dissection:** Angioplasty fractures the intimal plaque, allowing it to yield for vessel expansion. and the dissection planes may extend deep into the media (true dissection). In heavily fibrotic or calcified stenoses, dissections are necessary to allow the plaque to yield and prevent early recoil. Dissections are angiographically seen after ~30% of balloon angioplasties. Mild and shallow dissections (angiographic type A or B dissections) are not associated with worsened long-term outcomes. However, a severe dissection may obstruct the lumen within minutes to 24 hours after angioplasty; this occurs in 5–10% of angioplasties and is treated with bailout stenting.
 - **Elastic recoil** is the immediate vessel constriction that occurs after angioplasty. After the vessel appropriately yields to balloon inflation, it may quickly constrict upon balloon deflation (within 10 minutes). More prolonged inflation of the vessel with an appropriately sized balloon (sized 1:1 to the reference luminal diameter) at a high pressure reduces this phenomenon.
 - **High risk of restenosis** (~40%). Restenosis starts beyond the first month and is mainly due to **negative remodeling**, which is a form of late vessel constriction (as opposed to elastic recoil, a form of early vessel constriction).
- **Types of Balloons:**
 - **Non-compliant balloons** do not expand much beyond their nominal size even at high pressures (< 10% overexpansion), allowing one to exert high pressure across a calcified, unyielding lesion without balloon overexpansion across the soft spots. However, **compliant balloons** are low pressure and conform to the lumen size.

- **Scoring Balloon:** balloon that is scored with blades (cutting balloon) or wires (Angiosculpt) allows the plaque to yield more easily, at lower inflation pressures. Theoretically, this increases the success of angioplasty and may be associated with less severe dissections. Also, a scored balloon is less likely to slip during balloon inflation. Standard, non-scored balloons tend to slip when inflated across a heavily fibrotic stenosis (“watermelon seeding”). Using longer balloons, slower inflation, and scored balloons reduces this phenomenon.
- **Drug Coated Balloons (DCB):** DCBs are designed and created to carry antiproliferative drug such as paclitaxel or sirolimus that is delivered to the vessel wall when inflated, thereby preventing neointimal hyperplasia.
- **Indications:** Cases where plain balloon angioplasty is sometimes performed, without stenting:
 - Vessels < 2.0 mm.
 - Bifurcation lesions, in which a diseased side branch is dilated while the main branch is stented.
 - Treatment of DES restenosis.

Percutaneous Coronary Intervention

Bare-metal stents (BMSs):

A stent addresses all three balloon angioplasty pitfalls. It covers and seals the dissection planes or, at least, prevents them from expanding and promoting abrupt vessel closure. It has enough radial strength to prevent early (elastic recoil) and late (restenosis) vessel constriction.

The stent is mounted on a compliant balloon and is apposed to the vessel wall through balloon inflation. Prior to advancing a stent, lesion pre-dilatation with a slightly undersized balloon breaks the fibrosis and calcium, which allows stent delivery and expansion. Sometimes, “direct stenting” not preceded by balloon angioplasty may be performed.

Factors favoring successful direct stenting are: Absence of calcium at the target or other coronary vessels, absence of severe proximal tortuosity, non-critical stenosis, and age < 70 years.

The stent is usually deployed at a pressure ≤ 14 atm to prevent edge overinflation by the compliant stent balloon and the risk of edge dissection.

After stent deployment, stent dilatation may be performed with a shorter non-compliant balloon placed within the stent and inflated at a higher pressure (15–18 atm) to ensure proper stent expansion.

▪ **Pitfalls:**

- **Stent thrombosis:** while preventing abrupt vessel closure, stenting is associated with a risk of stent thrombosis, mainly in the first month. This risk is 0.5–1% in patients receiving DAPT with aspirin and clopidogrel, and 5–10% in patients receiving single antiplatelet therapy with aspirin.
- **In-stent restenosis (ISR):** restenosis is reduced to 20–25% with stenting. Overall, stenting eliminates the late negative remodeling seen after plain angioplasty, but increases the degree of neointimal hyperplasia, which starts 1 month after stenting and progresses for up to 6–8 months. The rate of clinical restenosis after BMS, i.e., angina recurrence, is ~15%.

Drug-eluting stents (DESs):

A DES consists of a stent platform similar to a BMS, with two additional components: a **drug**, and a **polymer** that controls the local drug delivery over 3–6 months.

- **First-generation DESs:** sirolimus [Cypher] and paclitaxel [Taxus, Ion];
- **Second-generation DESs:** everolimus [Xience V, Promus, Synergy], zotaralimus [Resolute]).

The drug inhibits cell proliferation and thus neointimal hyperplasia, with a restenosis rate of <5–10%. On the other hand, by delaying stent strut coverage, the risk of stent thrombosis persists beyond the first month. With the first-generation DESs, this risk of stent thrombosis remained significant for the first 12 months and mandated DAPT for 12 months. The second-generation DESs are associated with a dramatic reduction in the risk of stent thrombosis and target vessel MI (vs. first-generation DESs); the risk of stent thrombosis is very low even after clopidogrel interruption at 3–6 months.

DES is superior to BMS in all subsets of patients.

Rotational atherectomy (Rotablator) and orbital atherectomy:

As opposed to angioplasty, which expands the media without affecting plaque volume, atherectomy acts by removing plaque; it cuts the atheroma into small microparticles that are subsequently eliminated by the reticuloendothelial system. Those microparticles are typically very small, smaller than the red blood cells, and thus do not usually plug the microcirculation, as long as each atherectomy pass is limited to < 30 sec and vasodilators are used between passes.

Atherectomy is useful in heavily calcified lesions that do not yield with high-pressure balloon angioplasty, meaning that the balloon never fully expands across the lesion. A stent should never be used for a lesion where the balloon does not fully expand, as the stent will fail to appropriately expand, and a catastrophic stent thrombosis may occur.

- **Rotational Atherectomy:**

- Mechanism of Action: The principal mechanism for rotational atherectomy (RA) is differential cutting in which the diamond-tipped burr (available in sizes 1.25 to 2.50 mm at 0.25 mm increments) drills through rigid atherosclerotic plaque and calcium but spares the underlying elastic arterial structure.
- Indications: Most commonly it is used to prepare vessels with severe fibrocalcific disease where otherwise balloons or stents could not be passed. After balloon angioplasty fails to expand a lesion, the patient is brought back 4-6 weeks later for rotational atherectomy. It is not performed in a patient with dissection planes soon after angioplasty, as a major vessel perforation may be created by atherectomy.
- Contraindication:
 - Angulation of more than 60 degrees is a relative contraindication for RA, and bends of more than 90 degrees have a strong contraindication.
 - A lesion that is more than 25 mm in length has a relative contraindication for RA. However, if RA is being considered for these patients, a smaller burr size should be used.
 - A reduced ejection fraction (LVEF < 30%) was previously a contraindication to RA, but the advent of mechanical support devices has allowed physicians to consider RA in selected patients.

- **Orbital Atherectomy:**

- The Diamondback 360-degree OA system uses a diamond-coated crown (available in sizes 1.25 to 2.00 mm at 0.25 mm increments) that orbits eccentrically over a coil made of three spiral wires. The operator should ensure the presence of calcium on both sides of the arterial wall using fluoroscopy or a 270-degree arc of calcium within the plaque via intravenous ultrasound (IVUS).
- Difference between RA and OA:
 - The elliptical motion of the crown makes deeper cuts and can ablate plaque in both antegrade and retrograde fashion and, at the same time, allows for greater blood flow and heat dissipation during atherectomy.
 - The risk of entrapment of the device on the plaque is theoretically lower and the sanding motion results in smaller particulate matter.
 - Unlike the RA system where the adequacy of flushing is determined by the operator, the OA system requires a continuous flow of flush and automatically disables if the flow is interrupted.
 - Finally, the preferred motion for the OA crown is slow continuous advancement as opposed to the pecking motion preferred for RA.

Aspiration thrombectomy:

As an adjunct to balloon and stenting, aspiration thrombectomy catheters (suction catheters: Export, Pronto catheters) can be used to aspirate thrombi.

Aspiration thrombectomy catheters have been mainly studied at a large scale in acute STEMI. Initial data suggested that they improve microcirculatory and cellular perfusion (TAPAS trial). However, large trials (TASTE and TOTAL) did not show any clinical benefit from the systematic use of thrombectomy and there was a small stroke hazard. The selective use of thrombectomy in STEMI patients with a large thrombus burden may still be justified.

Stent thrombosis, restenosis, and neoatherosclerosis:

▪ **Stent thrombosis:**

- Stent thrombosis usually occurs within 1 month of stent placement but can occur later with DES or BMS. It is prevented with DAPT and adequate stent expansion. Stent thrombosis typically leads to STEMI, the prognosis of which is much worse than that of spontaneously occurring STEMI (high clot burden), with a 15–45% risk of mortality.
- Timing of stent thrombosis: Acute (within 24 hours); Subacute (between 1 and 30 days); Late (between 1 and 12 months); and Very late (> 12 months).

After the first month, stent thrombosis usually occurs ≥ 7 days after clopidogrel discontinuation, implying that brief clopidogrel interruption for non-cardiac surgery may be safe.

○ **Risk factors for stent thrombosis:**

- **Mechanical:** Stent underexpansion, stent malapposition, edge dissection, edge plaque shift (especially if the plaque is necrotic and active)
- **Pharmacological:** Acutely, a delayed loading of ADP receptor DAPT is a risk factor for acute thrombosis. Non-compliance with the recommended duration of DAT is the most important risk factor for subacute and late stent thrombosis. Clopidogrel non-responsiveness increases the risk of stent thrombosis, which is rarely a standalone factor in stent thrombosis.
- **Underlying patient and lesion:** ACS presentation, particularly STEMI, is by far the most important predictor of stent thrombosis. Other factors: diabetes, renal failure, small vessel, long lesion, poor runoff and bifurcation PCI.

▪ **Restenosis:**

• **Mechanisms:**

- **After plain balloon angioplasty:** (i) Negative arterial remodeling (arterial constriction): the main mechanism; (ii) Neointimal hyperplasia. Both processes start beyond 1 month (1–6 months).
- **After stenting:**

- Stent underexpansion (suboptimal stent deployment): When the stent is underexpanded, even a mild degree of neointimal hyperplasia may lead to significant restenosis.
- Neointimal hyperplasia refers to smooth muscle cell and macrophage migration from deep in the vessel wall (media) to the surface of the struts. This is followed by cellular proliferation and production of extracellular matrix (fibrosis).
Neointimal hyperplasia starts to develop 1 month after angioplasty or stent placement, and peaks at 3–6 months. Neointimal hyperplasia is milder after DES but also more delayed than after BMS.
- **Patterns of restenosis:** Restenosis may be focal (42% of cases of BMS restenosis), diffuse (21%), proliferative (extends beyond stent margins; 30%), or totally occlusive (7%).
- **Clinical presentation:** Restenosis usually leads to recurrence of stable angina, but it may lead to MI presentation in ~10% of patients (usually NSTEMI). Therefore, while it is less catastrophic than stent thrombosis, restenosis is not benign.
- **Treatment:** *IVUS* helps determine the mechanism and guide the treatment of in-stent restenosis.
- Restenosis is treated with balloon angioplasty if the main problem is technical (i.e., the stent is underexpanded) or if the in-stent restenosis is focal.
- Conversely, diffuse in-stent restenosis and edge restenosis are treated with DES placement within the previously placed BMS or DES. Alternatively, a drug-coated balloon may be used.
- **Neoatherosclerosis**
Beyond 1 year, atherosclerosis starts to grow over the stent neointima; this is referred to as neoatherosclerosis. As opposed to neointimal hyperplasia, neoatherosclerosis is characterized by a lipid-laden plaque with foamy macrophages and a fibrous cap. It tends to appear earlier and more frequently with DES (30–50% at 1–2 years) than BMS (16% at 5 years). It explains *late restenosis* and partly explains the *very late stent thrombosis* seen with both types of stents.

Mechanisms of recurrent target vessel disease after stenting:

- **First 1-2 months:**

Mechanical issues leading to subacute stent thrombosis (acute severe presentation) or residual stenosis (insidious presentation): stent underexpansion, edge disease or edge dissection, failure to cover the entire target lesion.

- **1-12 months:**

- Stent restenosis
- Late stent thrombosis from stent underexpansion.
- Disease progression outside the stented area, especially at the edges (more so in ACS).

- **Over 1 year:**

- Neoatherosclerosis
- Late presentation of neointimal hyperplasia
- Disease progression outside the stented area

Complex lesion subsets:

- **Multivessel PCI:**

The presence of a chronic total occlusion or one or more technically difficult lesions or long lesions (angiographic SYNTAX score ≥ 23) should favor CABG, especially because CABG provides a more complete revascularization. Also, Diabetes favors CABG as CABG provides lower rate of repeat revascularization and better survival compared with PCI in diabetes.

- **Long lesions and diffuse disease (multiple lesions in series):**

Normally, the stent should be implanted from normal reference to normal reference if possible; this will avoid edge dissections and edge plaque shift.

In case of diffuse disease with tandem lesions in series, the most severe lesions are stented (spot stenting), while the intermediate ones may be left untreated. If possible, the distal lesion should be stented first, followed by the proximal lesion; this obviates the need to cross the proximal stent with the distal stent.

Very long stenting (“full metal jacket”), even with DES, is associated with a high risk of restenosis and is preferably avoided. Furthermore, long stenting may compromise future placement of bypass grafts and is preferably avoided, especially in the LAD.

▪ **Bifurcation lesions:**

Side branch (SB) narrowing may occur after main branch (MB) PCI. This is related to plaque shift (snowplow phenomenon). The likelihood of this depends on the degree of ostial SB narrowing. When the ostium of the SB has >50% stenosis (= true bifurcation lesion), there is a risk of SB occlusion with MB stenting (14–35%). Bifurcation stenoses are approached as follows:

- Double wiring, i.e., wiring of both SB and MB, is indicated when the SB is large (>2–2.5mm) *and* has significant disease. Occasionally, if the supplied territory is very large, SB is wired even in the absence of significant disease.
- Pre-dilate SB if it is significantly diseased at baseline or after MB dilatation.
- Avoid planned dual stenting (NORDIC, BBC-1, and CACTUS trials), except when SB is very large with diffuse (not just ostial) disease.
- Post-dilate SB *only if* occlusion, impaired flow, or \pm severe narrowing (>90%) develops (NORDIC 3 trial).
- Stent SB only in case of suboptimal balloon angioplasty result, i.e., one of the following four features: SB occlusion, poor flow, dissection, or \pm severe residual stenosis (>90%) in a large SB. SB is more readily post-dilated or provisionally stented when it is large (e.g., LCx in distal left main stenting). After dual stenting, final kissing balloon inflation is necessary to resolve MB stent distortion.

FFR studies have shown that SB narrowing that occurs after stenting is often functionally non-significant. The narrowing is partly due to a benign geometric kinking of SB when MB is straightened by the stent.

Stent-induced occlusion of a large branch may result in significant myocardial ischemia, though in most patients the long-term prognosis is good and many initially occluded SBs are patent on follow-up.

▪ **Chronic total occlusion (CTO):**

CTO is defined as a total occlusion that is > 3 months old without any antegrade filling (true CTO), or with faint antegrade filling through microchannels (functional CTO).

An occlusion may develop progressively over time and lead to an insidious, chronic angina presentation.

Well-developed collaterals may provide flow equivalent to a 50–90% stenosis, which helps maintain myocardial viability and prevents resting myocardial ischemia. When the coronary occlusion develops progressively rather than abruptly, the

myocardial function may be normal at rest or depressed, but not infarcted (hibernating rather than necrotic myocardium). Hibernation is distinguished from infarction by the persistence of angina, lack of Q waves, lack of echocardiographic thinning, and the presence of ischemia on stress testing.

CTO PCI is indicated in symptomatic patients who have a large ischemic burden on stress testing, especially if symptoms or ischemia are refractory to medical therapy. The success rate of CTO PCI can exceed 80% when using a hybrid algorithm, with mortality rates of 0–2%. Restenosis rate is markedly reduced with DES (~10%).

Five main features predict failure of the antegrade approach to CTO PCI:

1. Heavy calcification across the CTO.
2. Sharp angle/tortuosity > 45° within the CTO site.
3. Presence of a side branch at the occlusion point without any stump (the wire will preferentially go into the side branch).
4. Long CTO > 2-3 cm.
5. Presence of a network of thin collaterals around the occlusion (caput medusa). These may be hard to distinguish from intraluminal microchannels, which, to the contrary, predict a high success rate.

CTO with antegrade, microchannel flow is called functional CTO; the vessel continues to opacify past the CTO in an antegrade fashion. Polymer-coated wires may be used in a functional CTO to slide through the microchannels. Otherwise, drilling wires with progressively heavier tips are used, with the support of a catheter advanced to the occlusion site.

Double arterial access with engagement of the contralateral coronary is usually necessary. Contralateral injections allow collateral retrograde filling of the index vessel and thus proper visualization of the wire progression. Antegrade vessel opacification usually ceases once the wire and catheter are advanced to the CTO site, making contralateral guidance critical in most cases.

PCI complications:

- **Mortality**: Mortality after diagnostic angiography is ~0.1%, but this increases significantly in severe AS or left main disease (up to 0.5%). Mortality after PCI is < 1% (~0.5%).
Complications and mortality after PCI are related to:
 - **Patient characteristics**: ACS presentation, unstable hemodynamics/emergent case, severe HF or severe LV dysfunction, older age, CKD.
 - **Lesion characteristics**: severe calcifications, tortuosity, multivessel CAD, CTO, degenerated venous graft (especially left venous graft, where guide support is difficult).
- **Coronary dissection**:
A coronary dissection is seen after 30% of balloon angioplasties.
It may also occur at the edges of a stent, when over inflation of the stent's balloon damages the edges. It may also result from wire manipulations or from a deep-seated guiding catheter. Dissections typically propagate distally.
- **Angiographic types of coronary dissection**
 - **Type A**: luminal haziness that does not persist after dye clearance.
 - **Type B**: parallel tract or double lumen does not persist after dye clearance.
 - **Type C**: extraluminal dye stain that persists after dye clearance (different from thrombus, where the stain is intraluminal). It looks angiographically similar to a type 1, localized perforation.
 - **Type D**: spiral luminal filling defect that *significantly narrows* the true lumen. Flow may be slow but completely fills the artery.
 - **Type E**: luminal filling defect with incomplete distal flow.
 - **Type F**: total occlusion.
- **Treatment**:
 - When occurring after plain balloon angioplasty, types A and B dissections are often benign and do not affect outcomes; they may be treated with prolonged low-pressure balloon dilatation.

- Whether with angioplasty or stenting, angiographic dissections types C through F carry an increased risk of thrombosis and vessel closure and are treated with further stenting.

Stent distally to stop the propagation of the dissection, then proximally to seal the source of dissection. When the guide dissects the ostial left main or RCA and leads to hemodynamic compromise, proximal stenting may need to be performed first to relieve the extent of ischemia.

In small or severely tortuous vessels where stenting is not possible, perform prolonged low-pressure balloon inflation with a well-sized balloon (not undersized).

- Since type C dissection may be a localized perforation that manifests 24–48 hours later, the patient needs to be monitored and an echo needs to be repeated 24 hours later, looking for hemopericardium.

- **Intramural hematoma** is a bleeding inside the media that displaces the internal elastic membrane inward without a dissection entry or exit point.

On IVUS, it appears like a deep medial dissection without superficial extension. Angiographically, it may simulate a dissection or may appear smooth, ***simulating a refractory spasm***.

It is usually treated with further stenting at a low pressure.

- **Periprocedural MI:**

- Periprocedural MI occurs in 5–10% of PCI cases and the incidence is reduced with the current antiplatelet regimens. It is often the result of:

- abrupt vessel closure, thrombus formation, or occlusion of a major side branch.
- Distal microembolization, microvascular spasm, and microcellular reperfusion injury in a successfully opened vessel. A sluggish flow in spite of a patent artery (TIMI 2 flow or less) is called ***no reflow***.
- Loss of small side branches.
- Transient procedural complications, such as thrombus or flow-limiting dissection.

No reflow is reduced with the use of GPIIb–IIIa inhibitors, and with the use of filter devices during venous graft interventions.

Once it occurs, it is treated with intracoronary adenosine, verapamil, or nitroprusside.

▪ **Coronary perforation:**

○ **Causes:** A coronary perforation may be secondary to:

- Wire tip tearing the distal end of a branch, especially when a polymer wire is advanced too deeply.
- Balloon or stent inflation. This is more common with an oversized balloon, especially in a calcified vessel.
- Rotablator perforation, usually the largest perforation.

○ **Classification:**

- **Concealed perforation (type 1)** manifests as an extraluminal stain.

It requires no specific treatment except monitoring.

- **Limited perforation (type 2)** manifests as a myocardial or epicardial blush/stain without jetting.

It can usually be managed with prolonged balloon inflation (≥ 5 min) at the perforation site or just proximal to it. An echo is performed and repeated 24 hours later.

- **Freeflowing, jet-like dye streaming (type 3).** The streaming may be pericardial, leading to immediate tamponade, or ventricular, better tolerated hemodynamically.

○ **Management:** Two procedures are to be immediately and concomitantly performed:

(1) Pericardiocentesis, and

(2) Prolonged balloon inflation proximal to the perforation site. Afterwards, a second femoral access (7 or 8 Fr) is obtained and a second guiding catheter is used to double-engage and double-wire the perforated coronary artery. A Graftmaster covered stent is advanced through the second guiding catheter while the balloon is still inflated through the first guiding catheter, the balloon being only briefly deflated to advance the covered stent to the perforation site.

- Emergent surgery may be required if the perforation fails to seal with balloon inflation and a covered stent cannot be used.
- A non-sealing perforation of a branch or distal vessel, which is usually a wire-induced perforation, may be treated by distal injection of thrombin, *small coils* or *small fat particles* harvested from the femoral access site (cut into pieces < 1 mm and mixed with saline).

- **Femoral access complications:** All femoral bleeding complications are increased with PCI (vs. diagnostic catheterization), female sex, higher anticoagulant dose, GPI therapy, and HTN.
- **Groin hematoma:** A large hematoma is a hematoma that is associated with a significant drop in hemoglobin, a requirement for transfusion, or hemodynamic compromise. It may lead to nerve compression and neurological symptoms (femoral or lateral cutaneous nerve).
- **Retroperitoneal hematoma (~0.7% of PCIs):** due to injury of the external iliac artery dives deep in the loose pelvis and is not compressible, even at its distal part.
 Such a bleed should be immediately considered in a patient with flank or back pain, unexplained bradycardia or vagal shock, or unexplained tachycardia or hypotension that does not quickly improve with fluid administration and atropine (if appropriate), and without a large superficial hematoma.
 After initial quick fluid resuscitation, the patient with persistent, unexplained hypotension is urgently taken back to the cath lab and a contralateral access obtained. Iliac angiography is obtained and, if contrast extravasation is seen, a prolonged balloon inflation is performed. This may be followed by placement of a covered stent across the perforation.
- **Femoral pseudoaneurysm:** A pseudoaneurysm is an expansile collection of blood that has two features differentiating it from a hematoma: (i) It is not clotted, and (ii) It remains in communication with the arterial lumen, i.e., there is active bleeding.
 In contrast, a hematoma is clotted blood without active bleeding. A pseudoaneurysm must be distinguished from a hematoma (exam, ultrasound), as it is an active bleed that will continue to expand.
 A bruit is heard on exam and a pulsatile mass is felt. The diagnosis is made by ultrasound Doppler, which shows a mass that communicates with the femoral artery through a *to-and-fro, high turbulence flow*.
 The risk is higher with a low superficial femoral or profunda stick, as those arteries are not supported by bony structures and are difficult to compress; the profunda, in particular, dives posteriorly and deeply into the thigh, immediately upon takeoff, making it prone to uncontrollable bleed or pseudoaneurysm.

A pseudoaneurysm that is < 3.5cm with a small neck (less than a few millimetres) is treated with ultrasound-guided prolonged compression (45 min) or ultrasound-guided thrombin injection. A large pseudoaneurysm > 3.5 cm, a pseudoaneurysm with a large neck, or a pseudoaneurysm that fails thrombin therapy is corrected surgically.

- **Arteriovenous fistula:**

The risk is increased when the access is low, at the superficial femoral or profunda level, or when a venous sheath is used along with the arterial sheath. Below the femoral bifurcation, the femoral veins cross over to become anterior then lateral to the arteries, rather than medial, and risk getting punctured on the way to the arterial access.

A continuous femoral bruit is heard. At least one-third of fistulas close within 1 year, mostly within 4 months. The remaining fistulas tend to remain stable without complications on 1-year follow-up, as these fistulas are usually small.

Monitoring is usually the first line of therapy, with serial clinical and ultrasound follow-ups every 3 months. Surgical correction is indicated in case of progressive growth or complications (limb ischemia, DVT, HF).

- **Limb ischemia:**

Limb ischemia may be related to impairment of flow by the sheath itself in patients with a small or diseased femoral artery. If limb ischemia is not promptly corrected by sheath removal, a femoral dissection, thrombus, or distal embolization should be suspected.

Heparin is administered and a femoral ultrasound is urgently performed, followed by urgent vascular surgery (for exploration and thrombectomy) or percutaneous intervention through a contralateral access.

- **Contrast-induced nephropathy (CIN):**

CIN is defined as either a 25% increase in serum creatinine from baseline or a 0.5 mg/dL increase in absolute SCr value within 48-72 hours after intravenous contrast administration.

The incidence is ~3–5%, but is higher in the case of: Pre-existing renal failure, HF (or worse, shock), dehydration, or diabetes with renal failure (diabetes alone is not a risk factor) or high contrast load (> 3× the GFR in ml/min) or multiple contrast studies within 72 hours.

Most contrast nephropathies eventually improve at 1 week and renal function returns to baseline. However, 18% are left with some irreversible impairment of renal function.

Prevention of contrast nephropathy:

- The Mehran Score is used to predict the risk of CIN after PCI.
- Hydration with normal saline (better than 0.45% saline), 1 ml/kg/hr for 12-24 hours before the procedure and 12 hours after the procedure. *In HF with clinical or hemodynamic congestion, hydration aggravates volume overload and may potentially worsen the risk of renal impairment.*
- Use the smallest amount of contrast (30ml for a diagnostic coronary angiogram, if possible; total contrast < 2-3 × GFR for PCI).

▪ **Stroke:**

Periprocedural incidence: 0.07% after routine diagnostic cardiac catheterization, up to 1% after crossing the aortic valve in severe AS, up to 0.4% after PCI.

Ischemic stroke is related to atheroembolization of aortic plaques, embolization of thrombi formed on the wires/catheters, or embolization of an LV thrombus. This risk increases with age, peripheral arterial disease, or venous graft interventions. Patients with prior CABG generally have heavy aortic atherosclerosis; in addition, difficult left venous graft engagement and retrograde embolization during ostial venous graft intervention may lead to stroke.

Hemorrhagic stroke is rare and may be related to anticoagulation.

▪ **Cholesterol atheroembolization:**

Atheroembolization may occur in patients with severe aortic or iliac atherosclerosis, who slough off cholesterol debris during the procedure.

This may lead to distal cyanosis (blue toes), livedo reticularis, subacute progressive renal failure (occurring > 1 week later, with eosinophiluria), and mesenteric ischemia.

Intracoronary Imaging

- The arterial wall has three layers (from inwards to outwards): Intima, Media, and Adventitia. In normal vessels, the intima is very thin, thinner than the media. In atheromatous arteries, the intima is essentially composed of atheroma, and its thickness corresponds to the plaque thickness; the media undergoes atrophy and becomes thinner than the intima.
- In the presence of atherosclerosis, the media undergoes expansion in such a way that the luminal area remains normal. This is called **positive remodeling** or the Glagov phenomenon. However, ~10–20% of atherosclerotic vessels undergo **negative remodeling**, wherein the media constricts and further narrows the lumen beyond what is expected from atherosclerosis. Thus, *luminal narrowing depends on the amount of atherosclerosis but also the type and extent of remodeling*.
- The spatial resolution of intravascular imaging (IVI) is dependent on the wavelength and beam-width. However, tissue penetration is determined by frequency, and as frequency is increased, penetration distance is decreased.
- Imaging should be performed after administration of intracoronary nitroglycerine and should begin 20 mm or more distal to the area of interest and end at the LM or RCA ostium using either manual pull back (more common) or mechanical pull back.

Intravascular Ultrasound (IVUS)

IVUS is a sound-based adjunctive imaging modality that employs the use of an intravascular catheter mounted with a piezoelectric crystalline transducer to generate ultrasound pulses to provide real-time 360-degree cross-sectional images. Transmitted ultrasound waves from this device are reflected differentially across varied tissue structures in vivo (e.g., echogenic structures, such as fibrous tissue and calcifications, produce brighter hyperechogenic signals, whereas echolucent structures, such as lipid collections, produce low-intensity hypoechogenic signals) and are then generated into a gray-scale, cross-sectional image of the target vessel.

IVUS offers characterization of intracoronary pathology, plaque morphology, and vessel wall architecture.

- **Preparation:**

- As air reflects ultrasound before it can reach tissue structures, air-bubble artifacts generated between the catheter sheath and the IVUS transducer can degrade IVUS images, and thus, careful catheter flushing and preparation outside the body before use is essential.
- Because of a blood stasis artifact, the lumen may look white and “hazy” and the lumen-intima boundary may be blurry, making luminal measurement difficult or may be confused with a thrombus or with an echolucent intima (e.g., lipid-rich intima or intima with a necrotic core) falsely suggesting unstable disease. In order to improve blood stasis artifact, flush the coronary artery with contrast or saline whenever there is luminal blurriness.
- **Image analysis:**
 - When one is looking at an IVUS image, the first step is to find the black band inside the arterial wall. This black band is the media; inside it, are the intima and the lumen.
 - Vascular structures seen in the surroundings of the imaged artery may be arterial branches (e.g., septal, diagonal branches) or coronary veins. If, upon pullback, the structure enters the intima and joins the main vessel, the structure is a branch. Otherwise, it is a vein. Arterial branches are useful landmarks that identify the disease location and correlate it with angiography. Also, in the case of dissection, if the wire position is in question (true lumen vs. false lumen), seeing branches that join the lumen confirms the true luminal position of the wire.
 - **Plaque types:** IVUS identifies three types of plaques (i.e., three types of intima):
 1. **Echolucent, soft intima** is less echogenic (less white) than the adventitia. A soft plaque may be hard to differentiate from a hazy lumen.
 2. **Echodense, fibrous intima** is as bright as or brighter than the adventitia. Most atherosclerotic lesions are fibrous.
 3. **Calcified intima** is brighter than the adventitia and has deep shadowing. The calcium is quantified by the arc it encompasses (e.g., 90°, 180°) and its depth. Superficial calcium is defined as calcium in the top half of the intima and is particularly adverse to stent expansion.
- **Basic IVUS measurements:** The following are basic IVUS measurements:

- **External elastic membrane (EEM) cross-sectional area (CSA)**, also called total vessel CSA: EEM corresponds to the outer boundary of the media. This is the boundary between the black band (media) and the outer adventitia.
- **Minimal luminal area [MLA]**: Lumen CSA at the level of the stenosis. This is the most important measurement and the one correlating the most with outcomes.

Contrary to a common misconception, the area of stenosis does not reference the stenosis to the EEM area. Alternatively, *MLA should be compared to the most normal surrounding lumen.*

Conversely, referencing the plaque to the EEM area is called **plaque burden** or percent cross-sectional narrowing and is dependent on the amount of atheroma.

- In patients with a stent, the **stent area** is the area bounded by the stent struts, while the neointimal hyperplasia area is equal to stent area - lumen area.

The stent should be sized to the reference lumen area, not the EEM area. The stent should be sized to 100% of the distal reference or 90% of the average proximal and distal references. Sizing the stent to the EEM area results in stent oversizing with a risk of perforation or edge dissection.

An undersized stent is a stent with an area that is less than the reference lumen area.

A stent is underexpanded when:

- It is appropriately sized but the minimal stent area (MSA) (i.e., the stent area in the tightest spot) is less than the reference lumen area.
- The diameter of the stent is less than the nominal stent diameter (e.g., a 3 mm stent is only expanded to 2.5 mm).
- It is asymmetric with a minimal-to-maximal stent diameter < 0.7 .

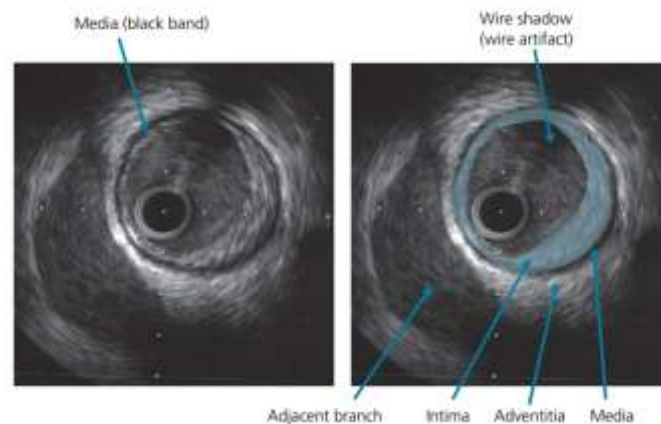


Figure 10-1: The left image is duplicated on the right with blue shading highlighting the intima. A wire artifact is seen as a black shadow. An adjacent vessel is seen. The imaged vessel is the proximal LAD and the adjacent vessel is the ramus. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

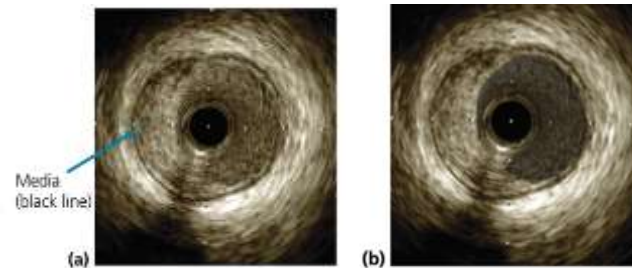


Figure 10-2: (a) Intima is marked in blue in the right-hand image. Note that the lumen is hazy, and one cannot definitely rule out echolucent (dark) plaque within this lumen. (b) After flushing the lumen, its boundaries become sharper, which makes luminal and intimal calculations easier and rules out echolucent plaque or intraluminal thrombus. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Optical Coherence Tomography (OCT)

- OCT catheters are designed to emit and receive near-infrared light waves -through a rotating single optical fiber coupled with an imaging lens- which are then digitally converted into real-time high spatial and contrast resolution, cross-sectional, and 3-dimensional volumetric images.
- OCT has the highest resolution among currently available IVI modalities -nearly 10 times greater than that of IVUS- at the expense of lower penetration depth (1-2 mm for OCT vs 5-6 mm for IVUS).
- The use of OCT technology is predicated on “bloodless” imaging. Specifically, light waves are attenuated by blood, and therefore, adequate image acquisition can only be obtained when the target vessel has been cleared of blood (typically by contrast) via either hand or power injection. This contrast injection requirement can lead to limitations utilizing OCT to adequately evaluate certain lesion subsets, such as ostial lesions (caused by admixture with blood), excessively large or small vessels, and severe stenoses, which may not adequately opacify with contrast medium unless specialized techniques are used.
- OCT has both high spatial resolution and ability to characterize the lumen-intima interface with detailed assessment of plaque morphology. Current OCT systems (by employing automated pull back) also allow accurate assessments of lesion length and further capitalize upon the increased spatial resolution of the technology to generate automated measurements of luminal dimensions.
- **On OCT**, the intima is yellow, the media is dark lucent, and the adventitia is often not visualized (when visualized, adventitia is dark red).

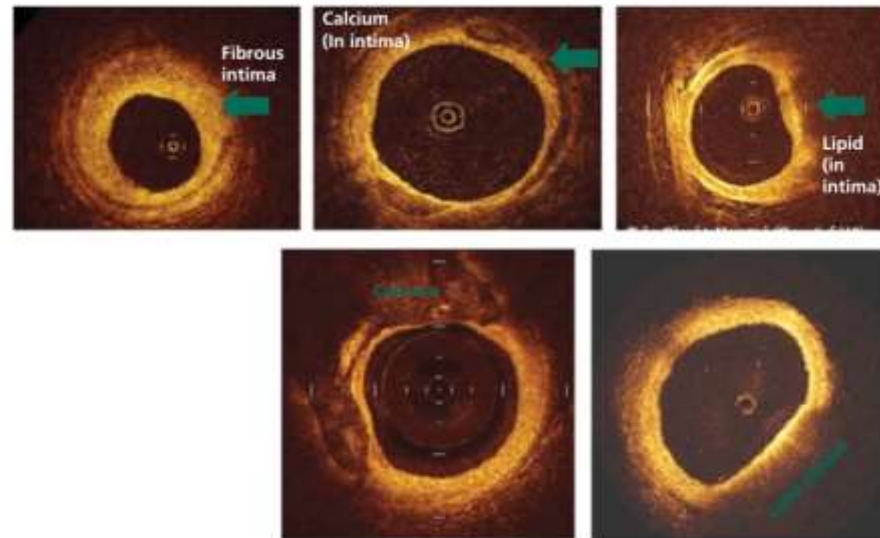


Figure 10-3: OCT. *Fibrotic plaque* is characterized by being bright (high signal). As opposed to IVUS, *calcium* on OCT is dark (low signal) and is well demarcated with low attenuation of light, allowing deeper imaging. *Lipid plaque* is dark but attenuates light more than calcium, which explains the loose edges and the shadowing; it is homogeneous. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Table 10-1: Comparison of IVUS and OCT Imaging Modalities

| IVUS | | OCT |
|---|-----------------------------------|--------------------------------|
| Energy source | Ultrasound | Near-infrared light |
| Wavelength, μm | 35-80 | 1.3 |
| Resolution, μm | 40-200 (axial); 200-300 (lateral) | 15-20 (axial); 20-40 (lateral) |
| Maximum scan diameter, mm | 15 | 7 |

| | | |
|-------------------------------|--|--|
| Tissue penetration, mm | 10 | 1-2.5 |
| Blood clearing | Not required | Required |
| Advantages | <ul style="list-style-type: none"> - IVUS does not require the use of contrast for blood clearance and is therefore advantageous for imaging in aorto-ostial lesions or in clinical scenarios, such as CTO revascularization, where pressurization of the lumen by contrast injection could be deleterious. - The longer wavelengths allow for favorable imaging in larger vascular structures (e.g., left main coronary artery) because of enhanced tissue penetration in noncalcified vessels. - The advantages afforded by not requiring contrast injection can be specifically helpful in treating patients with chronic kidney disease. | <ul style="list-style-type: none"> - Better definition of the intima, media, and fibrous cap (compared to IVUS). - Better assessment of plaque composition than IVUS (lipid-rich plaque vs. fibrous plaque). - Better visualization of thrombus than IVUS. - The greater resolution of OCT enables precise location of side branches, wire location, and stent visualization (including assessments of malapposition), with greater sensitivity to detect intimal/medial dissections. - As light (as opposed to ultrasound) is not attenuated by calcium, OCT uniquely affords the ability to measure the thickness of calcium in heavily calcified stenoses. |
| Disadvantages | Inferior detection of stent malapposition and edge dissections. | Cannot accurately assess residual plaque burden at stent edges. |

Near-Infrared Spectroscopy (NIRS)

NIRS is a unique IVI modality that relies on the property of substances to absorb and scatter near-infrared light (wavelengths from 800 to 2,500 nm).

NIRS systems are comprised of a scanning near-infrared laser, a pull back and rotation unit, and a traditional IVUS-sized catheter, and utilize electromagnetic radiation to characterize the chemical composition of tissues based upon differential light absorption in the near-infrared spectrum.

Software within the console analyzes captured spectral data and produces a color-coded graphical representation of the chemical composition of interrogated tissue called a chemogram. NIRS thus allows for characterization of the chemical composition of intravascular structures of interest—such as to quantify and qualify lipid distribution (eg, lipid core burden index). Notably, the finding of significant lipid content and plaque burden > 70% has been associated with a greater incidence of nonculprit lesion events.

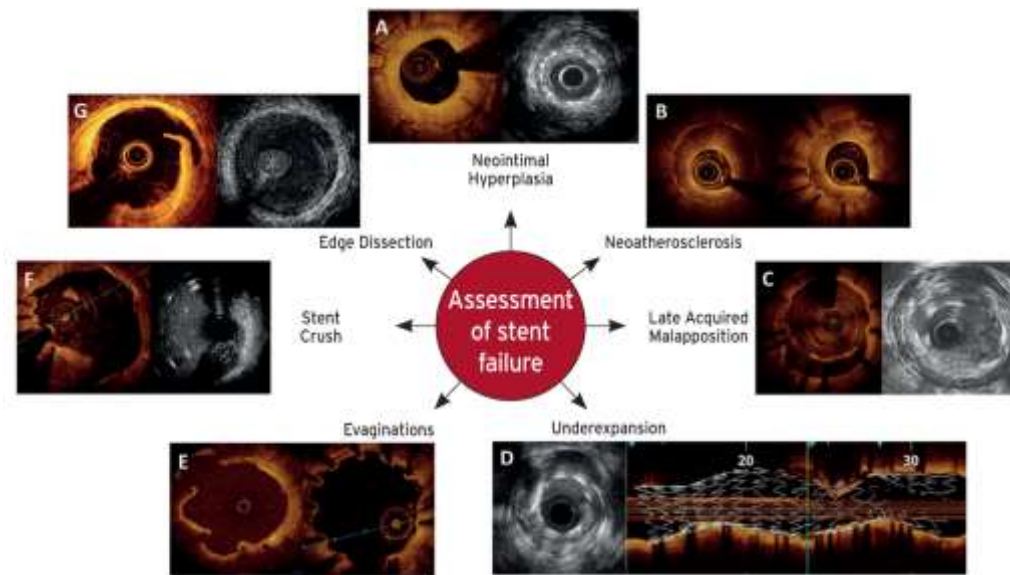


Figure 10-4: Intracoronary imaging for the assessment of stent failure. Examples of intravascular imaging findings (IVUS or OCT) in patients with stent failure. **Panel A:** displays OCT (left) and IVUS (right) examples of in stent restenosis due to excessive neointimal hyperplasia. **Panel B:** displays two OCT examples of in stent restenosis due to neoatherosclerosis. **Panel C:** displays OCT (left) and IVUS (right) examples of late acquired malapposition. **Panel D:** displays IVUS (left) and longitudinal OCT reconstruction (right) images of stent underexpansion. **Panel E** displays two OCT examples of in stent evaginations, a typical finding of delayed arterial healing. **Panel F** displays F displays OCT (left) and IVUS (right) examples of Stent crush. **Panel G** displays OCT (left) and IVUS (right) case of coronary dissection at the stent edge. **Source:** 2018 ESC/EACTS Guidelines on myocardial revascularization.

Physiologic assessment of coronary artery disease

Fractional flow reserve (FFR)

- **FFR concept and application:**

FFR is measured using a 0.014" coronary pressure wire which has a micromanometer 3 cm from its floppy tip (at the junction of the radiopaque distal tip and the radiolucent part of the wire).

This wire is advanced into the coronary artery and measures pressure distal to the stenosis (**Pd**). This pressure is compared to the aortic pressure (**Pa**) obtained through the guiding catheter.

In a simplistic way, FFR compares pressure distal to the stenosis to pressure in the aorta (Pd/Pa) under maximal hyperemia.

The drop in flow across a stenosis corresponds to:

- The severity of luminal narrowing,
- The length of stenosis,
- The extent of viable myocardium supplied by the artery, and
- The presence of collaterals.

For example, A 75% mid-LAD lesion supplying a normal anterior wall is more likely to be significant than a 75% small diagonal stenosis or 75% mid-LAD stenosis supplying an infarcted anterior wall.

Since myocardial flow= microvascular flow= pressure/microvascular resistance, maximal microcirculatory vasodilatation needs to be achieved in order to make pressure correlate linearly with flow.

In a patient with a significant stenosis, flow may be normal at rest but does not increase enough with maximal vasodilatation; thus, vasodilatation allows the calculation of the maximum achievable flow ratio (corresponding to exertional flow).

The preferred hyperemic stimulus is **intravenous adenosine** administered through a central venous line or a large antecubital vein.

- **Before adenosine administration**, The FFR number obtained is simply a drop in pressure across a stenosis and does not correspond to a drop in flow; "baseline pressure ratio".

- **After adenosine infusion**, the myocardial flow increases because of microcirculatory dilatation, the pressure further drops across the lesion, and, more importantly, this additional pressure drop correlates with an actual flow drop, i.e., FFR.
 - **FFR < 0.75** is hemodynamically significant and accurately identifies ischemia on non-invasive stress testing with 100% specificity.
 - **FFR > 0.80** has a sensitivity of > 90 % for excluding ischemia.
 - **FFR = 0.75 : 0.80**, ischemia is present but clinical variables are necessary to guide revascularization.
- **Special situation:**
 - **Serial stenosis:** Place the wire distal to all lesions and assess the summation FFR.
 If $\text{FFR} \leq 0.80$, perform a wire pullback maneuver under steady-state hyperemia (intravenous adenosine infusion) and assess the local pressure drop, i.e., flow drop, across each lesion.
 Treat the lesion with the highest focal drop, then reassess FFR to see if the remaining lesion is focally significant. After treating one of the lesions, the flow increases, which leads to further pressure drop across the other lesion, and as a result the true FFR across this other lesion will be lower than initially expected.
 - **Diffuse disease:**
 If $\text{FFR} \leq 0.80$ but pressure pullback reveals a gradual decline in pressure without a focal drop, the patient may not be served by revascularization. This may be seen in patients with mild or moderate diffuse disease and small coronary arteries.
 - **Ostial disease:**
 If the guiding catheter is too deeply engaged in a patient with ostial disease, the pressure at its tip corresponds not to the aortic pressure but to the pressure distal to the lesion.
 In this case, both the guiding catheter tip and the pressure wire sensor are distal to the stenosis. The guiding pressure (false Pa) and the sensor pressure (Pd) correlate closely and the FFR is falsely increased.
 Thus, while the guide may be temporarily engaged during wiring, it must be disengaged when FFR measurements are obtained.

On the other hand, when assessing a coronary lesion in a patient who has moderate ostial disease or a small ostium that damps upon guide engagement, deep guide seating creates an ostial obstruction and prevents maximal hyperemic flow, and thus maximal pressure drop at the level of the lesion (serial stenoses concept). *FFR at the level of the lesion is, again, falsely increased. Guide pressure (Pa) ventricularization at rest or with hyperemia is a hint to this phenomenon.* The guide needs to be withdrawn in the aorta during FFR measurement.

- **Value of FFR in assessing residual ischemia and viability:**

When part of the territory supplied by a coronary artery is infarcted, this territory receives reduced myocardial flow, and thus the maximal achievable flow across this myocardial territory is reduced. Also, as opposed to a viable myocardium, the hyperemic response of a chronically infarcted myocardium is impaired.

For example, suppose that a patient with no history of anterior MI has a 70% mid-LAD stenosis and FFR 0.70. If that same patient with the same LAD stenosis has a history of MI with necrosis of three-quarters of the supplied territory, FFR may end up being ~0.85, and *there may not be a significant difference between the resting and hyperemic pressure ratio (impaired microcirculation).*

It has been shown that patients who are positive for residual ischemia after MI, as assessed by nuclear imaging, have lower values of FFR compared to patients without residual ischemia. In the infarcted territory, FFR < 0.75 identifies residual ischemia that is completely reversible with stenting with a specificity of 100% and a sensitivity of 87%.

- **FFR vs. nuclear perfusion imaging in multivessel disease:**

Myocardial perfusion imaging (MPI) techniques are based on the concept of relative flow reserve (i.e., comparison of hyperemic flow in a stenotic artery vs. hyperemic flow in a non-stenotic artery) and require the presence of at least one normal vascular bed to demonstrate ischemia.

A nuclear substudy of the FAME trial found that in patients with angiographic multivessel disease, ~50% of vessels with FFR < 0.80 were not identified on nuclear imaging, and *34% of patients with ischemia by FFR had a negative nuclear scan.*

- **Left main disease: FFR and IVUS:**

- The assessment of left main lesion severity by angiography is subject to large inter- and intra-observer variability, particularly for 30-60% stenoses.
- In left main disease, several prospective studies have shown that deferral of CABG based on FFR > 0.80 is associated with good long-term outcomes, similar to the outcomes of patients with left main FFR ≤ 0.80 who receive CABG.
- IVUS may be used to guide left main revascularization. However, various studies have provided various cutoffs for what should be considered significant left main disease. While one retrospective study found that the lack of revascularization of a stenotic left main artery with a minimal lumen area < 7.5 mm² was associated with poor outcomes, other studies have found different cutoffs, such as a minimal lumen area < 6 mm², or a minimal lumen diameter < 2.5 mm.
- The functional significance also depends on the patient's original left main diameter and the presence of branch vessel disease (LAD or LCx disease). Additionally, the lack of coaxiality and the potential oblique luminal distortion may overestimate the minimal luminal area. Hence, IVUS of the LM should be performed from two different angles, one through an LAD wire and the other through an LCx wire.
- FFR seems to provide a more uniform and reproducible assessment of the significance of left main disease, but FFR has limitations as well: the frequent presence of concomitant lesions in the LAD, LCx, or both interferes with an isolated evaluation of the left main lesion. *Left main FFR is falsely increased in the presence of severe LAD or LCx disease (serial stenoses concept)*; this is particularly important in patients with proximal LCx disease and no LAD disease, in whom the referral to CABG is based on left main disease.

Procedural aspects of CABG

| Table 10-2: ESC Recommendations on procedural aspects of CABG: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| General considerations: | | |
| Complete myocardial revascularization is recommended. ⁽¹⁾ | I | B |
| Minimization of aortic manipulation is recommended. | I | B |
| Routine intraoperative graft flow measurement should be considered. | IIa | B |
| CT scans of the ascending aorta should be considered in patients over 70 years of age and/or with signs of extensive generalized atherosclerosis. | IIa | C |
| Prior to aortic manipulation, epiaortic ultrasound should be considered to identify atheromatous plaques and select the optimal surgical strategy. | IIa | C |
| Conduit selection: | | |
| Arterial grafting with IMA to the LAD system is recommended. | I | B |
| An additional arterial graft should be considered in appropriate patients. | IIa | B |
| The use of the radial artery is recommended over the saphenous vein in patients with high-grade coronary artery stenosis. ⁽²⁾ | I | B |
| BIMA grafting should be considered in patients who do not have a high risk of sternal wound infection. ⁽³⁾ | IIa | B |

- (1) **Anatomical complete revascularization** was defined as PCI or bypass of all epicardial vessels with a diameter exceeding ≥ 1.5 mm and a luminal reduction of $\geq 50\%$ in at least one angiographic view. **Functional complete revascularization** is achieved when all lesions causing resting or stress-induced ischaemia are bypassed or treated by PCI.
- (2) Particularly in patients with poor vein grafts. The radial artery should not be used if previously catheterized, if the Allen test is positive or if calcific degeneration is present.
- (3) Patients with DM, chronic pulmonary obstructive disease, previous mediastinal radiation, and obesity, particularly when multiples of these are present.

| | | |
|---|------------|----------|
| Vessel harvesting: | | |
| <i>Skeletonized IMA dissection is recommended in patients with a high risk of sternal wound infection.</i> | I | B |
| <i>Endoscopic vein harvesting, if performed by experienced surgeons, should be considered to reduce the incidence of wound complications.</i> | IIa | A |
| <i>No-touch vein harvesting should be considered when an open technique is used.</i> | IIa | B |
| Minimally invasive techniques: | | |
| <i>Off-pump CABG and preferably no-touch techniques on the ascending aorta, by experienced operators, are recommended in patients with significant atherosclerotic aortic disease.</i> | I | B |
| <i>Off-pump CABG should be considered for subgroups of high-risk patients by experienced off-pump teams.</i> | IIa | B |
| <i>Where expertise exists, minimally invasive CABG through limited thoracic access should be considered in patients with isolated LAD lesions or in the context of hybrid revascularization.</i> | IIa | B |
| <i>Hybrid procedures, defined as consecutive or combined surgical and percutaneous revascularization, may be considered in specific patient subsets at experienced centres.</i> | IIb | B |
| Early post-operative ischaemia and graft failure | | |
| <p><i>Coronary angiography post-CABG is recommended for patients with:</i></p> <ul style="list-style-type: none"> <i>- symptoms of ischaemia and/or abnormal biomarkers suggestive of perioperative MI</i> <i>- ischaemic ECG changes indicating large area of risk.</i> <i>- new significant wall motion abnormalities.</i> <i>- haemodynamic instability.</i> | I | C |

| | | |
|--|-----|---|
| <i>It is recommended that either emergency reoperation or PCI is decided upon by ad hoc consultation in the Heart Team, based on the feasibility of revascularization, area at risk, comorbidities, and clinical status.</i> | I | C |
| Disease progression and late graft failure | | |
| <i>Repeat revascularization is indicated in patients with a large area of ischaemia or severe symptoms despite medical therapy.</i> | I | B |
| <i>If considered safe, PCI should be considered as first choice over CABG.</i> | IIa | C |
| Procedural aspects of repeat revascularization: | | |
| <i>IMA is the conduit of choice for redo CABG in patients in whom the IMA was not used previously.</i> | I | B |
| <i>Redo CABG should be considered for patients without a patent IMA graft to the LAD.</i> | IIa | B |
| <i>Distal protection devices should be considered for PCI of SVG lesion.</i> | IIa | B |
| <i>PCI of the bypassed native artery should be considered over PCI of the bypass graft.</i> | IIa | C |

Table 10-3: ESC Recommendations on the management of carotid artery diseases in patients undergoing CABG:

| Recommendations | Class | Level |
|---|-------|-------|
| <i>In patients scheduled for CABG, it is recommended that the indication (and if so the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.</i> | I | C |
| Preoperative strategies to reduce the incidence of stroke in patients undergoing CABG: | | |
| <i>In patients undergoing CABG, carotid DUS is recommended in patients with recent (< 6 months) history of stroke/TIA.</i> | I | B |

| | | |
|---|------------|----------|
| <i>In patients with no recent (< 6 months) history of TIA/stroke, carotid DUS may be considered before CABG in the following cases: age ≥ 70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit.</i> | IIb | B |
| <i>Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.</i> | III | C |
| In patients scheduled for CABG, with recent (< 6 months) history of TIA/stroke: | | |
| • <i>Carotid revascularization should be considered in patients with 50 - 99% carotid stenosis.</i> | IIa | B |
| • <i>Carotid revascularization with CEA should be considered as first choice in patients with 50 - 99% carotid stenosis.</i> | IIa | B |
| • <i>Carotid revascularization is not recommended in patients with carotid stenosis < 50%.</i> | III | C |
| In neurologically asymptomatic patients scheduled for CABG: | | |
| • <i>Carotid revascularization may be considered in patients with bilateral 70-99% carotid stenosis <u>or</u> 70-99% carotid stenosis and contralateral occlusion.</i> | IIb | C |
| • <i>Carotid revascularization may be considered in patients with a 70-99% carotid stenosis, in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke ⁽¹⁾, in order to reduce stroke risk beyond the perioperative period.</i> | IIb | C |
| • <i>Routine prophylactic carotid revascularization in patients with a 70-99% carotid stenosis is not recommended.</i> | III | C |

(1) Contralateral TIA/stroke, ipsilateral silent infarction on cerebral imaging, intraplaque haemorrhage or lipid-rich necrotic core on MRA, or any of the following US imaging findings: stenosis progression (> 20%), spontaneous embolization on transcranial Doppler, impaired cerebral vascular reserve, large plaques, echolucent plaques, or increased juxta-luminal hypoechogenic area.

Note on outcomes with various surgical grafts:

▪ **SVG failure:** SVG grafts occlude at the following rates: ~10% in the first month, 15-25% in the first year, and 50% at 10 years.

○ **Causes and histology of SVG failure:**

- **< 1 month** (often before hospital discharge): Graft thrombosis, or due to technical issues (anastomotic stenosis from the suture, SVG kinking or stretching).
- **1 month to 1-3 years:** Fibrointimal hyperplasia leads to peri-anastomotic or mid-graft stenosis (exposure of the vein to the arterial pressure leads to endothelial injury with formation of a hard neointima).
- **> 1-3 years:** Atherosclerosis (with similar risk factors to native atherosclerosis).

As compared with native atherosclerosis, SVG atherosclerosis is more extensive, friable, with more foam cells and no fibrous cap, and may be mixed with thrombi. Aggressive lipid lowering slows down this process.

○ **Treatment of SVG failure:**

- **In the first 30 days:**

ST elevation is often the result of venous graft thrombosis with distal embolization, which worsens the perfusion of a previously stable territory subtended by a stenotic artery or by collaterals.

Reoperation may need to be performed the first day after CABG; beyond the first day, angiography may be performed and potentially treat anastomotic SVG disease or native distal disease with PCI.

- **Beyond the first 30 days:**

when SVG disease develops, it is best to treat the native artery as long-term patency of SVG is low.

If the native artery is not amenable to PCI (CTO), SVG PCI is performed, unless the SVG is also chronically occluded, in which case medical therapy is the best option.

Patients with multiple failing SVGs and no patent graft to the LAD have an indication for redo CABG.

▪ **LIMA Failure:**

- LIMA graft is usually used as an in-situ graft: the distal part of the LIMA is connected directly to the LAD, while the proximal LIMA is not touched and remains connected to the subclavian artery.
- LIMA atherosclerosis is extremely uncommon, thus the excellent long-term patency of 90% at 10 years; a LIMA that is patent beyond the first few months post-CABG usually remains patent for life. LIMA has an intact internal elastic membrane that prevents smooth muscle migration and atherosclerosis.
- Early LIMA failure is possible, and is related to anastomotic fibrointimal hyperplasia or to poor LIMA development.
- Always attempt to use LIMA to the LAD, except in:
 - Emergent cases with hemodynamic instability, where SVG-to-LAD may be preferred, because SVG has a higher and more expeditious flow initially.
 - Patients with severe lung disease in order to avoid pleural dissection and the subsequent left pleural effusion.

N.B: Significant native proximal disease is necessary to allow SVG and, more particularly, LIMA and radial grafts to remain patent; a good native flow may impede LIMA or SVG flow, leading to thrombosis of the SVG or spasm of an arterial graft. In fact, bypassing a LAD that has < 50-60% stenosis leads to disuse atrophy of the LIMA or “string sign” in up to 80% of patients.

While LIMA does not develop atherosclerotic disease, ischemia of the LIMA territory may be caused by:

- Subclavian stenosis (the most common cause of LIMA ischemia). *The assessment of BP in both arms is critically important in CABG patients presenting with angina.*
- Atresia of the LIMA graft related to insignificant proximal LAD disease, poor distal LAD runoff, or subclavian stenosis.
- Stenosis of the LIMA-to-LAD anastomosis, which often occurs in the first 3-6 months and results from intimal hyperplasia. Since it is not due to an atherosclerotic process, plain angioplasty provides good long-term patency.
- Progression of native LAD disease distal to the anastomosis.
- If the LIMA’s intercostal branches are not clipped, the flow may be directed away from the LAD (steal phenomenon). However, this is an unlikely phenomenon, as the coronary flow is mainly diastolic.

Hybrid revascularization

Hybrid coronary revascularization (HCR) is defined as combined or consecutive procedures consisting of an internal mammary artery graft to the LAD and PCI to the other non-LAD vessels for the treatment of MVD.

The rationale for HCR is to combine the prognostic benefits of a LIMA for grafting of the LAD with the potential benefits of contemporary PCI with DES for disease in arteries that would otherwise be revascularized using vein grafts (which are prone to occlusion). There is limited evidence from RCTs to support hybrid revascularization. Clinical decision-making in this regard should involve the Heart Team.

Clinical criteria supporting an HCR strategy in ACS patients with an indication for CABG may include: **(1)** MVD with LAD suitable for CABG and non-LAD lesions suitable for PCI, **(2)** atheroma in the ascending aorta, **(3)** an unprotected left main coronary artery that is unsuitable for PCI, **(4)** complex LAD disease, **(5)** advanced age, **(6)** low LVEF ($\leq 30\%$), **(7)** frailty, **(8)** diabetes mellitus, **(9)** renal failure, **(10)** prior sternotomy, and **(11)** the lack of available bypass conduits.

Miscellaneous

Myocardial bridging

- The coronary arteries normally take an epicardial course over the surface of the heart, but they occasionally have an intramyocardial segment that may get compressed in systole and cause symptomatic ischemia. This is called “myocardial bridging,” and it is characterized by angiographic off-and-on narrowing of the intramyocardial segment by >70%, only during systole.

This phasic obstruction distinguishes bridging from spasm, which is present throughout the cardiac cycle.

- Bridging is seen in 2% of coronary angiograms and is almost always limited to the LAD. Intramyocardial coronary segments are even more commonly diagnosed on coronary CT, with a frequency of up to 25%.
- Since over 80% of the left coronary blood flow occurs during diastole, bridging does not usually cause ischemia and often does not explain chest pain. During tachycardia, systolic coronary flow gains more importance as systole occupies a larger part of the cardiac cycle, while stronger inotropism leads to a stronger squeeze of the bridged LAD with a spillover into diastole, which may lead to exertional ischemia. This explains that up to 20% of patients with bridging may have ischemia on stress testing. The combination of exertional angina, ischemia on stress testing, and bridging on angiography without obstructive CAD suggests the diagnosis of symptomatic myocardial bridging.
- Even when symptomatic, myocardial bridging is a very benign condition with a very low risk of MI.
- β -Blockers are the mainstay of therapy.
- Nitrates and diuretics aggravate bridging as they may lead to reflex tachycardia and increased inotropism. In fact, NTG administration is a useful diagnostic test during angiography, as it unveils the severity of bridging (opposite effect on vasospasm).

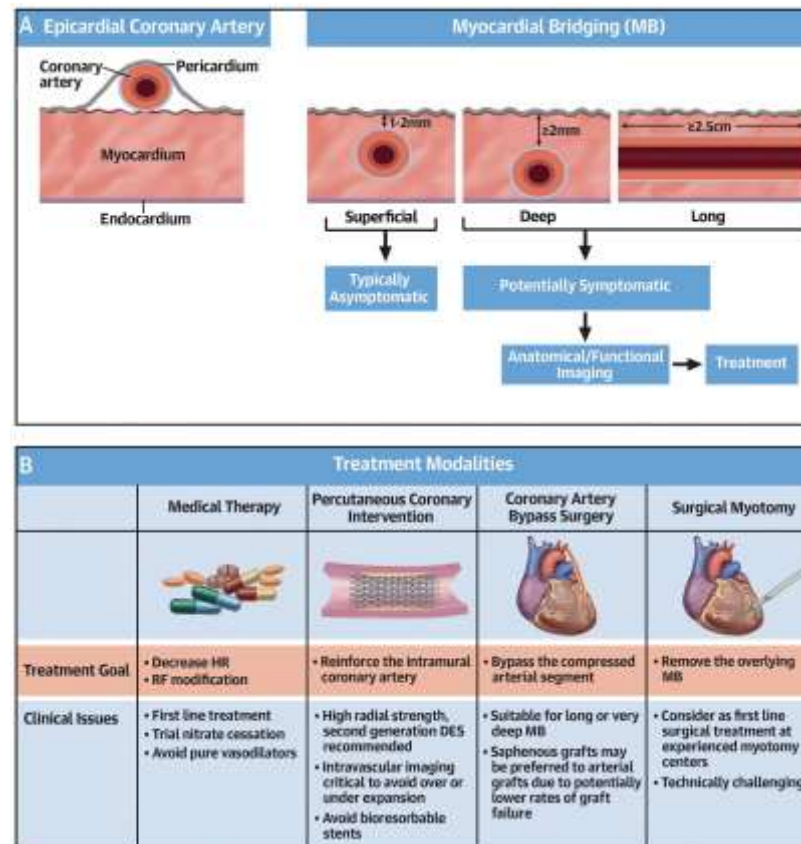


Figure 10-5: Anatomic properties of Myocardial bridging and overview of treatment modalities. Source: Sternheim D, Power DA, Samtani R, et al. Myocardial bridging: diagnosis, functional assessment, and management: JACC state-of-the-art review. Journal of the American College of Cardiology. 2021 Nov 30;78(22):2196-212.

Coronary collaterals:

Underdeveloped intercoronary channels often pre-exist in normal individuals before the occurrence of the coronary occlusion; coronary occlusion or severe stenosis leads to widening of these channels within the first 24 hours, followed by progressive enlargement and maturation of the collateral wall.

Mature collaterals that approximate 1mm in diameter with grade 3 filling of the recipient artery require > 1 day to form, typically 1–6 weeks.

In fact, half of patients with acute MI develop collateral flow in the first 6 hours, while all patients develop collaterals within 24 hours.

More mature collaterals may be seen early in MI if it was preceded by a chronic, severe coronary stenosis (e.g., $\geq 90\%$ chronic stenosis).

Intercoronary collaterals are angiographically graded as follows:

- **Grade 1**= side branch filling of the recipient occluded artery, without visualization of the body of the recipient artery;
- **Grade 2**= partial, faint filling of the body of the recipient artery; and
- **Grade 3** (mature collaterals)= complete filling of the recipient artery.

Nitric oxide promotes collateral growth; traditional risk factors, particularly diabetes, may impede the development of collaterals.

Hibernation, stunning, ischemic preconditioning:

- **Hibernation:** is chronic impairment of the myocardial function that results from a severe, persistent coronary stenosis; the myocardium downregulates its function and its metabolism to survive and remains viable. Chronic ischemia may, however, lead to irreversible fibrosis. The myocardial segment has reduced nuclear uptake at rest and with stress, but preserved metabolic uptake on PET study.
- **Stunning:** is transient myocardial dysfunction occurring after a severe, transient episode of ischemia. Ischemia resolves and leaves a viable myocardium that will recover in time. This is the case of an acutely occluded artery that is opened with PCI or

fibrinolytics (acute MI), exertional ischemia that occurs at stress and resolves at rest, or ischemia induced by cardiac surgery or PCI.

As opposed to hibernation, the artery is now open and there is no persistent ischemia, hence the stunned myocardium does not remain dysfunctional.

Unlike hibernation, the nuclear uptake is usually normal at rest. Repetitive stunning (exertional ischemia) can lead to persistent dysfunction and hibernation.

Recovery of function occurs 1–6 months after revascularization (faster with stunning, days to 1 month).

- **Ischemic preconditioning:** is the phenomenon whereby brief exposure to ischemia preconditions the heart and makes it more resilient to a later, prolonged and severe ischemia. In fact, ischemia stimulates protective myocyte receptors, such as adenosine receptors and G-protein receptors (protein kinase C). There are two windows of protection: the first starts within a few minutes of the brief ischemia and lasts a few hours; the second occurs at 24 hours and lasts 96 hours. This is partly why patients with pre-infarct angina suffer from smaller infarcts and have better outcomes.

SYNTAX score:

Table 10-4: Guide for calculating the SYNTAX score ⁽¹⁾:

| Steps | Variable assessed | Description |
|--------|-------------------------|---|
| Step 1 | Dominance | <i>The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.</i> |
| Step 2 | Coronary segment | <i>The diseased coronary segment directly affects the score as each coronary segment is assigned a weight depending on its location, ranging from 0.5 (i.e. the posterolateral branch) to 6 (i.e. left main in case of left dominance).</i> |

(1) SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

| | | |
|---------------|----------------------------|---|
| | | |
| Step 3 | Diameter stenosis | <p>The score of each diseased coronary segment is multiplied by two in case of a stenosis 50-99% and by five in case of total occlusion.</p> <p>In case of total occlusion, additional points will be added as follows:</p> <ul style="list-style-type: none"> • Age > 3 months or unknown +1 • Blunt stump +1 • Bridging +1 • First segment visible distally +1 per non-visible segment • Side branch at the occlusion +1 if <1.5 mm diameter +1 if both <1.5 mm and ≥1.5 mm +0 if ≥1.5 mm (i.e. bifurcation lesion) |
| Step 4 | Trifurcation lesion | <p>The presence of a trifurcation lesion adds additional points based on the number of diseased segments:</p> |

| | | |
|---------|---|---|
| | | <ul style="list-style-type: none"> • 1 segment +3 • 2 segments +4 • 3 segments +5 • 4 segments +6 |
| Step 5 | Bifurcation lesion | <p><i>The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification:</i></p> <ul style="list-style-type: none"> • Medina 1,0,0 - 0,1,0 - 1,1,0 +1 • Medina 1,1,1 - 0,0,1 - 1,0,1-0,1,1 +2 <p><i>Moreover, the presence of a bifurcation angle < 70 adds one additional point</i></p> |
| Step 6 | Aorto-ostial lesion | <i>The presence of aorto-ostial lesion segments adds one additional point</i> |
| Step 7 | Severe tortuosity | <i>The presence of severe tortuosity proximal of the diseased segment adds two additional points</i> |
| Step 8 | Lesion length | <i>Lesion length > 20 mm adds one additional point</i> |
| Step 9 | Calcification | <i>The presence of heavy calcification adds two additional points</i> |
| Step 10 | Thrombus | <i>The presence of thrombus adds one additional point</i> |
| Step 11 | Diffuse disease/ small vessels | <i>The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter < 2 mm) adds one point per segment number.</i> |

Important trials in coronary assessment and intervention:

| Table 10-5: Clinical trials in coronary assessment and intervention: | |
|--|---|
| Trial (date) | Summary |
| PCI Access: | |
| RIVAL (2011) | <p>Aim: To compare outcomes between radial and femoral access in patients undergoing cardiac catheterization for ACS.</p> <p>Study: 7021 patients presenting with NSTEMI-ACS and STEMI were randomized to either radial access or femoral access. Radial and femoral approaches are both safe and effective for PCI. However, the lower rate of vascular complications may be a reason to use the radial approach.</p> |
| MATRIX (2018) | <p>Aim: To compare outcomes between radial and femoral access in patients undergoing cardiac catheterization for ACS.</p> <p>Study: 8,404 patients with ACS were randomized to radial access versus femoral access. By factorial design, patients were also randomized to bivalirudin versus heparin. The primary outcome was death, MI, or stroke at 30 days. Radial access for cardiac catheterization was associated with a reduction in net adverse CV events compared with femoral access. Radial access was associated with a reduction in acute kidney injury compared with femoral catheterization. Radial access was associated with greater radiation to the operator and the patient.</p> |
| SAFARI-STEMI (2019) | <p>Aim: To assess whether there is a survival benefit when radial access is used instead of femoral access in patients referred for primary PCI.</p> <p>Study: 2,292 patients with STEMI undergoing primary PCI were randomized to radial access versus femoral access. All patients received aspirin 160 mg, P2Y12 inhibitor load, and UFH 60 U/kg (max 4000 U). The primary outcome was all-cause mortality at 30 days. The trial was terminated early due to futility in detecting a difference in the primary outcome. Radial access was not superior to femoral access.</p> |

| PCI Stents: | |
|----------------------------|--|
| RAVEL (2002) | <p>Aim: To compare sirolimus-eluting stent with uncoated stent in patients with angina pectoris.</p> <p>Study: 238 patients with a single de-novo coronary artery stenosis were randomized to implantation of a sirolimus-coated stent or of a standard stainless steel uncoated stent. The sirolimus-coated stent was designed to release 80% of the drug within 30 days from implantation. The primary end point was in-stent late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months). Sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis, and associated clinical events.</p> |
| TAXUS-IV (2004) | <p>Aim: To evaluate restenosis rates with the paclitaxel-eluting stent compared with bare stent in patients with single de novo coronary lesions.</p> <p>Study: 1314 patients with single de novo coronary lesions 10 to 28 mm in length, with reference-vessel diameter 2.5 to 3.75 mm, coverable by a single study stent, were prospectively randomized to the slow-release, polymer-based, paclitaxel-eluting stent or an identical-appearing bare-metal stent. The relative efficacy reported at 9 months for the paclitaxel-eluting stent compared with the bare-metal stent is preserved and continues to increase at 1 year, with no safety concerns apparent.</p> |
| NORSTENT (2016) | <p>Aim: To evaluate the long-term risks and benefits of the use of contemporary drug-eluting stents versus bare-metal stents.</p> <p>Study: 9013 patients who had stable or unstable coronary artery disease were randomly assigned to undergo PCI with the implantation of either contemporary drug-eluting stents or bare-metal stents. In the group receiving drug-eluting stents, 96% of the patients received either everolimus- or zotarolimus-eluting stents. The primary outcome was a composite of death from any cause and nonfatal spontaneous MI after a median of 5 years of follow-up. There were no significant differences between those receiving drug-eluting stents and those receiving bare-metal stents in the composite outcome. Rates of repeat revascularization were lower in the group receiving drug-eluting stents.</p> |

| | |
|-------------------------------------|---|
| EXAMINATION (2016) | <p>Aim: To evaluate the safety and efficacy of one of the second-generation stents (everolimus-eluting stent [EES]) versus BMS in patients presenting with STEMI.</p> <p>Study: 1504 STEMI patients scheduled for PCI within 48 hours of symptom onset (included primary PCI, rescue PCI, PCI after successful thrombolysis, and late comers [>12-48 hours]). Primary endpoints were all-cause mortality, any MI, any revascularization. The use of EES is similar to BMS for the composite clinical endpoint at 1 year, with a significant reduction in TLR/TVR and stent thrombosis at 1 year. On long-term follow-up, everolimus-eluting stent had a lower MACE rate than BMS, including mortality and TLR; stent thrombosis rates were similar after 1 year.</p> |
| COMFORTABLE-AMI (2019) | <p>Aim: To evaluate treatment with Biodegradable polymer DES compared with a bare-metal stent in patients with STEMI.</p> <p>Study: 2575 Patients with STEMI were randomized to a biolimus-eluting stent with biodegradable polylactic acid polymer versus a bare-metal stent. Aspiration thrombectomy was recommended prior to stent implantation. Primary endpoints were composite of CV death, target vessel reinfarction, or ischemia-driven target lesion revascularization. The use of a novel biolimus-eluting stent with biodegradable polymer was superior to a bare-metal stent.</p> |
| Functional assessment (FFR): | |
| FAME (2009) | <p>Aim: To compare treatment based on the measurement of FFR in addition to angiography with the current practice of treatment guided solely by angiography in patients with multivessel coronary artery disease for whom PCI is the appropriate treatment.</p> <p>Study: 1005 patients with multivessel coronary artery disease were randomly assigned to undergo PCI with DESs guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the $FFR \leq 0.80$. The primary endpoint was the rate of death,</p> |

| | |
|-----------------------------|--|
| | <i>nonfatal MI, and repeat revascularization at 1 year. Routine measurement of FFR in patients with multivessel coronary artery disease who are undergoing PCI with DESs significantly reduces the rate of the composite end point of death, nonfatal MI, and repeat revascularization at 1 year.</i> |
| FAMOUS-NSTEMI (2014) | <p>Aim: <i>To evaluate a FFR-guided strategy compared with a coronary angiography-guided strategy among participants with NSTEMI.</i></p> <p>Study: <i>350 participants with NSTEMI were randomized to an FFR-guided strategy versus a coronary angiography-guided strategy. FFR-guided strategy changed the initial treatment plan in approximately one-fifth of cases and resulted in a larger proportion of patients treated medically compared with an angiography-guided strategy. MACE were similar between treatment groups, although periprocedural MI tended to be higher in the angiography-guided group, and spontaneous MI tended to be higher in the FFR-guided group.</i></p> |
| COMPARE-ACUTE (2017) | <p>Aim: <i>To evaluate FFR-guided complete revascularization compared with IRA revascularization in patients undergoing primary PCI.</i></p> <p>Study: <i>885 patients with STEMI and multivessel disease who had undergone primary PCI of an IRA were randomly assigned to undergo complete revascularization of non-IRA guided by FFR or to undergo no revascularization of non-IRA. The addition of FFR-guided complete revascularization of non-IRA resulted in lowest risk of a composite CV outcome than the risk among those who were treated for the IRA only. This finding was mainly supported by a reduction in subsequent revascularizations.</i></p> |
| FLOWER-MI (2021) | <p>Aim: <i>To evaluate complete revascularization guided by FFR versus angiography in patients with STEMI who underwent PCI of culprit vessel.</i></p> <p>Study: <i>1,171 patients with STEMI and multivessel disease who had undergone successful PCI of the infarct-related artery were randomly assigned to receive complete revascularization guided by either FFR or angiography. In patients with STEMI undergoing complete revascularization, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial</i></p> |

| | |
|-------------------------------|--|
| | <i>infarction, or urgent revascularization at 1 year. However, given the wide confidence intervals for the estimate of effect, the findings do not allow for a conclusive interpretation.</i> |
| FRAME AMI (2023) | <p>Aim: <i>To compare FFR-guided PCI with angiography-guided PCI for non-IRA lesions among patients with acute MI and multivessel disease.</i></p> <p>Study: <i>562 Patients with acute MI and multivessel coronary artery disease who had undergone successful PCI of the infarct-related artery were randomly assigned to either FFR-guided PCI (FFR ≤ 0.80) or angiography-guided PCI (diameter stenosis of $>50\%$) for non-infarct-related artery lesions. The primary end point was a composite of time to death, MI, or repeat revascularization. In patients with acute MI and multivessel coronary artery disease, a strategy of selective PCI using FFR-guided decision-making was superior to a strategy of routine PCI based on angiographic diameter stenosis for treatment of non-infarct-related artery lesions regarding the risk of death, MI, or repeat revascularization.</i></p> |
| Intracoronary imaging: | |
| IVUS: | |
| IVUS-XPL (2015) | <p>Aim: <i>To determine whether the long-term clinical outcomes with IVUS-guided PCI are superior to those with angiography-guided PCI in patients with long coronary lesions</i></p> <p>Study: <i>1400 patients requiring long coronary stent implantation were randomly assigned to receive IVUS-guided or angiography-guided everolimus-eluting stent implantation. Primary outcome was the composite of MACE, including cardiac death, target lesion-related MI, or ischemia-driven target lesion revascularization at 1 year. The use of IVUS-guided stent implantation resulted in a significantly lower rate of the composite of major adverse cardiac events at 1 year. These differences were primarily due to lower risk of target lesion revascularization.</i></p> |
| ULTIMATE (2018) | Aim: <i>To evaluate IVUS-guided compared with angiography-guided PCI among an all-comers group of patients undergoing PCI.</i> |

| | |
|----------------------------------|--|
| | <p>Study: 1,448 patients undergoing coronary revascularization were randomized to IVUS-guided PCI versus angiography-guided PCI. IVUS-guided PCI was associated with a lower frequency of target vessel failure up to 3 years compared with angiography-guided PCI.</p> |
| <p>CTO-IVUS (2015)</p> | <p>Aim: to test the hypothesis that IVUS-guided CTO intervention is superior to angiography-guided intervention</p> <p>Study: 402 patients with CTOs were divided randomly into an IVUS-guided group and angiography-guided group. The primary endpoint is a composite of cardiac death, MI and target vessel revascularization at 12 month. Although IVUS-guided CTO intervention did not significantly reduce cardiac mortality, this randomized study demonstrated that IVUS-guided CTO intervention might improve 12-month major adverse cardiac event rate after new-generation drug-eluting stent implantation when compared with angiography-guided CTO intervention.</p> |
| <p>OCT:</p> | |
| <p>DOCTORS (2016)</p> | <p>Aim: To assess the efficacy of OCT in optimizing PCI among patients with NSTE-ACS.</p> <p>Study: 1935 patients with NSTEMI/ACS were randomized to either OCT-guided PCI or routine management/angiography-guided PCI. OCT-guided PCI results in a better functional outcome (as assessed by post-PCI FFR) compared with routine angiography-guided PCI in patients undergoing PCI of a single lesion for NSTEMI/ACS. There was a higher incidence of post-stent optimization procedures (such as overdilation and additional stent implantations) in the OCT arm. However, there was also higher contrast, radiation, and time utilization in the OCT group. The trial was not powered for clinical outcomes.</p> |
| <p>ILUMIEN III (2016)</p> | <p>Aim: to establish whether OCT-based stent sizing strategy would result in a minimum stent area similar to or better than that achieved with IVUS guidance and better than that achieved with angiography guidance alone</p> <p>Study: 415 patients had one or more target lesions located in a native coronary artery with a visually estimated reference vessel diameter of 2.25–3.50 mm and a length of less than 40 mm were randomly assigned to OCT guidance, IVUS guidance, or angiography-guided stent implantation. The primary efficacy endpoint was post-PCI minimum stent area, measured by OCT. The primary safety endpoint was procedural MACE. OCT-guided PCI</p> |

| | |
|-----------------------------------|---|
| | <i>using a specific reference segment external elastic lamina-based stent optimisation strategy was safe and resulted in similar minimum stent area to that of IVUS-guided PCI.</i> |
| OPINION (2017) | <p>Aim: <i>to demonstrate the non-inferiority of OFDI-guided PCI compared with IVUS-guided PCI in terms of clinical outcomes</i></p> <p>Study: <i>829 patients undergoing PCI with a second-generation drug-eluting stent were randomly assigned to OFDI vs. IVUS. The primary endpoint was target vessel failure defined as a composite of cardiac death, target-vessel related myocardial infarction, and ischaemia-driven target vessel revascularization until 12 months after the PCI. The 12-month clinical outcome in patients undergoing OFDI-guided PCI was non-inferior to that of patients undergoing IVUS-guided PCI. Both OFDI-guided and IVUS-guided PCI yielded excellent angiographic and clinical results, with very low rates of 8-month angiographic binary restenosis and 12-month target vessel failure.</i></p> |
| CABG: | |
| CABG vs medical treatment: | |
| STICH (2011) | <p>Aim: <i>To evaluate the role of CABG in the treatment of patients with coronary artery disease and LV systolic dysfunction.</i></p> <p>Study: <i>1212 patients with LVEF ≤ 35% and coronary artery disease amenable to CABG were randomly assigned to medical therapy alone or medical therapy plus CABG. There was no significant difference between medical therapy alone and medical therapy plus CABG with respect to the primary end point of death from any cause. Patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for CV causes.</i></p> |
| PCI vs CABG: | |
| SYNTAX (2009) | Aim: <i>To compare PCI and CABG for treating patients with previously untreated three-vessel or left main coronary artery disease (or both)</i> |

| | |
|-----------------------|--|
| | <p>Study: 1800 patients with three-vessel or left main coronary artery disease were randomly assigned to undergo CABG or PCI. CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined endpoint of major adverse cardiac or cerebrovascular events at 1 year.</p> |
| ASCERT (2012) | <p>Aim: To compare the rates of long-term survival after PCI and CABG.</p> <p>Study: Among 189,793 patients ≥ 65 years of age who had two-vessel or three-vessel coronary artery disease without acute MI, 86,244 underwent CABG and 103,549 underwent PCI. The median follow-up period was 2.67 years. There was a long-term survival advantage among patients who underwent CABG as compared with patients who underwent PCI.</p> |
| NOBLE (2016) | <p>Aim: To compare outcomes following CABG and PCI in patients with unprotected left main disease.</p> <p>Study: 1,184 patients with significant left main lesion were randomized to either PCI with DES or CABG; 88% of the DES were biolimus. CABG might be better than PCI for treatment of left main stem coronary artery disease.</p> |
| FREEDOM (2012) | <p>Aim: To compare multivessel PCI to CABG in diabetic patients on optimal medical therapy.</p> <p>Study: 1900 patients with diabetes and multivessel coronary artery disease were randomly assigned to undergo either PCI with drug-eluting stents or CABG. The patients were followed for a minimum of 2 years (median among survivors, 3.8 years). CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke.</p> |
| FAME 3 (2021) | <p>Aim: To demonstrate the noninferiority of FFR-guided PCI to CABG for patients with three-vessel disease.</p> <p>Study: 1500 patients with angiographic stenosis $\geq 50\%$ stenosis in three major epicardial vessels without left main involvement were randomized to either FFR-guided PCI or CABG. FFR-guided PCI using current-generation DES did not meet criteria for noninferiority compared with CABG among patients with angiographic three-vessel disease. Prior trials comparing PCI to CABG had used bare-metal stents or first-generation DES (SYNTAX) and did not incorporate systematic ischemic evaluation as was done here using FFR.</p> |

References and suggested readings:

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Section

III

Valvular Heart Diseases

TO THE POINT

Chapter 11

Valvular Heart Disease

Patient evaluation:

- **Clinical Evaluation:** Essential questions in the evaluation of patients for valvular intervention:
 - How severe is VHD?
 - What is the aetiology of VHD?
 - Does the patient have symptoms ?
 - Are symptoms related to valvular disease ?
 - Are any signs present in asymptomatic patients that indicate a worse outcome if the intervention is delayed?
 - What are the patient's life expectancy and expected quality of life ?
 - Do the expected benefits of intervention (versus spontaneous outcome) outweigh its risks?
 - What is the optimal treatment modality? Surgical valve replacement (mechanical or biological), surgical valve repair, or catheter intervention ?
 - Are local resources (local experience and outcome data for a given intervention) optimal for the planned intervention ?
 - What are the patient's wishes?

N.B: AHA/ACC Guidelines describe stages in the progression of VHD:

- **Stage A** (at risk): patients with risk factors for development of VHD
- **Stage B** (progressive): patients with progressive VHD (mild to moderate severity and asymptomatic)
- **Stage C** (asymptomatic severe): asymptomatic patients who meet criteria for severe VHD.
 - **C1:** asymptomatic patients with a compensated left and right ventricle
 - **C2:** asymptomatic patients with decompensation of the left or right ventricle
- **Stage D** (symptomatic severe): patients who have developed symptoms as a result of VHD

▪ **Transthoracic Echocardiography:**

- TTE is the key technique used to confirm the diagnosis of VHD and to assess its severity and prognosis.
- TEE is also key to assess valve morphology and function as well as to evaluate the feasibility and indications of a specific intervention.

• **Transesophageal echocardiography (TEE):**

- TEE is indicated in severe MR. It establishes the severity of MR, the anatomic cause of MR, the feasibility of mitral repair (cusps involved), and guides mitral repair.
- TEE is not superior to TTE in assessing the severity of AS or AI. In fact, it is difficult to get the aortic valve gradient by TEE. TEE is superior to TTE for the anatomic assessment of the aortic valve and for the diagnosis of endocarditis.
- TEE can identify a left atrial appendage thrombus in patients with MS or AF, the presence of which dictates the deferral of percutaneous valvuloplasty.
- **Intraoperative TEE** is indicated in all cases of valvular surgery, particularly mitral valve repair. It immediately detects a suboptimal result or postoperative technical problems. In the immediate preoperative setting, it should not be relied upon for the assessment of valvular disease severity, particularly functional MR, as general anesthesia decreases the cardiac loading conditions and may make valvular regurgitation appear less severe. A mild ischemic MR on preoperative TEE may actually be moderate or severe, especially during exertion.

▪ **Other non-invasive investigations:**

○ **Stress testing:**

- The primary purpose of exercise testing is to unmask the objective occurrence of symptoms in patients who claim to be asymptomatic. A functional capacity 1-2 METs below average ⁽¹⁾ is concerning for symptomatic valvular disease. It is especially useful for risk stratification in aortic stenosis.
- Exercise testing will determine the level of recommended physical activity, including participation in sports.

(1) Predicted METs= *For men:* $18 - (0.15 \times \text{age})$; *For women:* $14.7 - (0.13 \times \text{age})$.

- Exercise echocardiography may identify the cardiac origin of dyspnoea. Prognostic impact has been shown mainly for aortic stenosis and mitral regurgitation.
- The use of stress tests to detect CAD associated with severe valvular disease is discouraged because of their low diagnostic value and potential risks in symptomatic patients with aortic stenosis.
- **Cardiac MRI:**
 - In patients with inadequate echocardiographic quality or discrepant results, CMR should be used to assess the severity of valvular lesions, particularly regurgitant lesions, and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis.
 - CMR is the reference method for the evaluation of RV volumes and function and is therefore particularly useful to evaluate the consequences of tricuspid regurgitation.
- **Cardiac CT:**
 - CCT may contribute to the evaluation of valve disease severity, particularly in aortic stenosis and possibly associated disease of the thoracic aorta (dilatation, calcification), as well as to evaluate the extent of MAC.
 - CCT should be performed whenever the echocardiographic data indicate an aortic enlargement > 40 mm, to clarify aortic diameter and to assess aortic morphology and configuration.
 - CCT is essential in the pre-procedural planning of TAVI and can also be useful to assess patient-prosthesis mismatch.
 - It is also a prerequisite for pre-procedural planning of mitral and tricuspid valve interventions.
- **Positron emission tomography (PET)/CCT** is useful in patients with suspicion of prosthetic valve endocarditis.
- **Cinefluoroscopy:** Cinefluoroscopy is particularly useful for assessing the kinetics of the leaflet occluders of a mechanical prosthesis.
- **Biomarkers:** BNP levels, corrected for age and sex, are useful in asymptomatic patients and may assist selection of the appropriate time for a given intervention, particularly if the level rises during follow-up.
- **Invasive investigations:**

- **Coronary angiography:** CA is recommended for the assessment of CAD when surgery or an intervention is planned, to determine if concomitant coronary revascularization is recommended. Alternatively, owing to its high negative predictive value, CCT may be used to rule out CAD in patients who are at low risk of atherosclerosis.
The presence of CAD dictates a combined CABG + valvular surgery. Beside being an appropriate therapy for CAD, CABG reduces the risk of postoperative infarction and LV failure. CA may be forgone in emergency situation (acute regurgitation, endocarditis, aortic dissection).
- **Cardiac catheterization:** The measurement of pressures and cardiac output or the assessment of ventricular performance and valvular regurgitation by ventricular angiography or aortography is restricted to situations where noninvasive evaluation by multimodality imaging is inconclusive or discordant with clinical findings. Right heart catheterization is also indicated in patients with severe tricuspid regurgitation as Doppler gradient may be impossible or underestimate the severity of pulmonary hypertension.

Management of associated conditions:

▪ Management of CAD:

| Table 11-1: ESC Recommendations for management of CAD in patients with VHD: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Diagnosis of CAD: | | |
| Coronary angiography is recommended before valve surgery in patients with severe VHD and any of the following: | I | C |
| <ul style="list-style-type: none"> - In men > 40 years of age <u>and</u> postmenopausal women. - One or more cardiovascular risk factors. - History of cardiovascular disease. - Suspected myocardial ischaemia (Chest pain, abnormal non-invasive testing). - LV systolic dysfunction. | | |

| | | |
|---|-----|---|
| Coronary angiography is recommended in the evaluation of severe SMR. | I | C |
| Coronary CT angiography should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD. ⁽¹⁾ | IIa | C |
| Indications for myocardial revascularization: | | |
| CABG is recommended in patients with a primary indication for aortic/mitral/tricuspid valve surgery and coronary artery diameter stenosis $\geq 70\%$ ⁽²⁾ | I | C |
| CABG should be considered in patients with a primary indication for aortic/mitral/tricuspid valve surgery and coronary artery diameter stenosis $\geq 50-70\%$. | IIa | C |
| PCI should be considered in patients with a primary indication to undergo TAVI or transcatheter mitral valve intervention and coronary artery diameter stenosis $> 70\%$ in proximal segments. | IIa | C |

▪ **Management of AF:**

| Table 11-2: ESC Recommendations on management of atrial fibrillation in patients with native VHD: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Anticoagulation: | | |
| For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation. | I | A |
| The use of NOACs is not recommended in patients with AF and moderate to severe mitral stenosis. | III | C |
| Surgical interventions: | | |

(1) Coronary CT angiography may also be used in patients requiring emergency surgery with acute infective endocarditis with large vegetations protruding in front of a coronary ostium.

(2) Stenosis $\geq 50\%$ can be considered for left main stenosis. FFR ≤ 0.8 is a useful cut-off indicating the need for an intervention in patients with mitral or tricuspid diseases, but has not been validated in patients with aortic stenosis.

| | | |
|---|------------|----------|
| <i>Concomitant AF ablation should be considered in patients undergoing valve surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (LA dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors)</i> | Ila | A |
| <i>LAA occlusion should be considered to reduce the thromboembolic risk in patients, with AF and a CHA₂DS₂VASc score ≥ 2 undergoing valve surgery.</i> | Ila | B |

Endocarditis prophylaxis:

Antibiotic prophylaxis should be considered for high-risk procedures in patients with prosthetic valves, including transcatheter valves, or with repairs using prosthetic material, and in patients with previous episode(s) of infective endocarditis.

Particular attention to dental and cutaneous hygiene and strict aseptic measures during any invasive procedure are advised in this population.

Antibiotic prophylaxis should be considered in dental procedures involving manipulation of the gingival or periapical region of the teeth or manipulation of the oral mucosa.

Prophylaxis for rheumatic fever:

- Prevention of rheumatic heart disease should preferably target the first attack of acute rheumatic fever. Antibiotic treatment of group A Streptococcus infection throat is key in primary prevention.
- In patients with established rheumatic heart disease, secondary prophylaxis against rheumatic fever is recommended: benzathine benzylpenicillin 1.2 MUI every 3 to 4 weeks over 10 years.
- Lifelong prophylaxis should be considered in high-risk patients according to the severity of VHD and exposure to group A Streptococcus.

Mitral stenosis

Aetiology:

- Mitral stenosis (MS) is usually secondary to **rheumatic fever** and occurs a couple of decades after the initial infection, as the injured valve gets progressively traumatized by the turbulent blood flow.
Rheumatic MS is more common in *women* (2:1), and occurs at a *young age* in *third-world countries*.
- Other rare causes of MS:
 - **Mitral annular calcification** (MAC) or senile MS: MAC occurs with age, Hypertension and particularly common in end-stage renal disease. MAC initially develops at the *posterior annulus* without causing any inflow obstruction, then progress to involve the base of both mitral leaflets and the papillary muscles; the valvular edges remain freely mobile. This is opposite to rheumatic MS, which starts at the valvular edges and commissures.
Severe MAC may lead to mild or moderate MS, but also MR, as MAC impairs the overall leaflet mobility and coaptation. Calcifications may also extend into the mitroaortic interannular fibrosa and tricuspid annulus (Lenègre-Lev disease ⁽¹⁾).
Since MAC does not consist of commissural fusion, valvuloplasty is not an effective therapy.
 - **Rheumatic-like inflammatory process**: rheumatoid arthritis, lupus, carcinoid syndrome.
 - **Parachute mitral valve**: Congenital MS usually consists of a single papillary muscle to which all chordae converge. This chordal convergence restricts valvular opening. It usually presents early in life.

Natural history:

- The fibrotic process initially involves the mitral commissures and the leaflet edges, and manifests as commissural fusion. The process then progressively involves the whole valve and subvalvular apparatus with progressive calcifications.

(1) Lev's disease is an acquired complete heart block due to idiopathic fibrosis and calcification of the electrical conduction system of the heart. Lev's disease is most commonly seen in the elderly, and is often described as senile degeneration of the conduction system.

- The subvalvular apparatus may shorten and pull on the leaflets, creating rheumatic MR beside MS.
- Symptoms progress more slowly than with other valvular disorders (it takes 5-10 years to progress from early functional class II to functional class III-IV).
- Without surgical or percutaneous therapy for class II or III symptoms, the survival is ~50% at 10 years, which is low yet better than other valvular disorders left untreated. However, class IV patients have a mean survival of < 1 year without invasive therapy.

Diagnosis:

▪ **Transthoracic Echocardiography:**

TTE is the preferred method for diagnosis, assessment of severity, and haemodynamic consequences of mitral stenosis. Clinically significant mitral stenosis is defined by a mitral valve area (**MVA**) $\leq 1.5 \text{ cm}^2$. Valve area using **2D planimetry** is the reference measurement of mitral stenosis severity, whereas mean transvalvular gradient and pulmonary pressures reflect its consequences and have a prognostic role.

Echocardiographic features:

- Early on, the commissures are fused and the free edges are immobilized, while the body of the anterior leaflet is free-moving. This gives the anterior mitral leaflet a hockeystick shape. The posterior leaflet appears stiff, immobile.
- Commissural fusion \pm commissural calcium are seen on the mitral short-axis view and lead to a “fish mouth” shape of the mitral orifice.
- The valve and subvalvular apparatus are thick \pm calcified. The chordal thickening is particularly well visualized on the apical views.
- On the mitral valve M-mode, the E-F slope is flattened because there is no diastasis in mid-diastole. The posterior leaflet is pulled towards the anterior leaflet because of the commissural fusion.

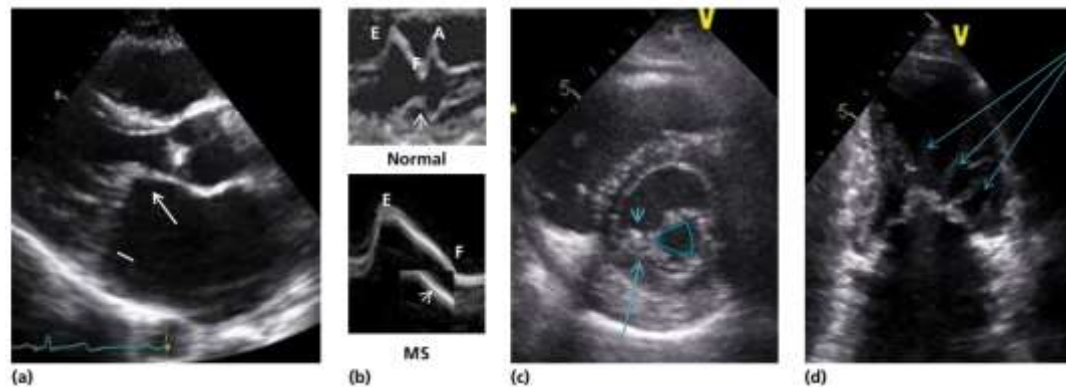


Figure 11-1: (A) Long-axis view in diastole. See the hockeystick shape of the anterior leaflet (*arrow*), the tip of which looks attached to the stiff posterior leaflet (*line*), with no diastolic opening. In fact, **both leaflets are tied together by the commissural fusion**. **(B) M-mode across the mitral valve.** The E–F slope is flattened and the posterior leaflet is dragged towards the anterior leaflet (*arrowhead*). **(C) Commissural fusion on the mitral short-axis view** (*arrow*). Commissural calcium is seen (*arrowhead*). Rather than oval, the mitral opening has a “fish mouth” shape. **(D) Apical four-chamber view shows severe chordal thickening extending to the papillary muscles** (*arrows*). The mitral leaflets are thickened, and the thickening and immobility extend beyond the edges into the body of the leaflets. The Wilkins score is 10 (leaflet thickness=2, calcium=2, leaflet mobility=2, chordal thickening=4). **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

N.B:

- ☞ The estimation of the mitral valve area (MVA) using one of the four echo methods (mitral inflow pressure half-time, continuity equation, PISA method, and planimetry) may be subject to measurement errors, and thus MVA is better assessed with invasive hemodynamics.
- ☞ *MVA is a better determinant of MS severity than the mitral gradient.* In fact, transmitral pressure gradient being proportional to the square of the transmitral flow per second, tachycardia or a high-output state (e.g., anemia, heavy vasodilator use, sepsis) may convert an *anatomically mild MS* into a *hemodynamically severe MS* with a *severely increased transmitral gradient*. Hence,

in any echo or invasive study of MS, it is always important to report the heart rate. Heart rate reduction and diuresis may be appropriate first-line therapies in an anatomically mild MS, which underlines the importance of invasive assessment of cardiac output and MVA in selective cases. Overall, invasive hemodynamics are valuable for the assessment of MS whenever there is discrepancy between the echocardiographic MVA and transmitral gradient; and whenever it is not clear whether the patient's symptoms or pulmonary hypertension are purely secondary to MS, or rather secondary to mild MS in addition to high-output state, tachycardia, or LV diastolic dysfunction. *The invasive calculation of MVA and cardiac output is invaluable in these cases, and is often performed in patients whose echocardiographic MVA is in the mild or moderate range.*

Echocardiographic Wilkins score:

The Wilkins score is an assessment of the severity of the valvular and subvalvular distortion and a rough estimate of suitability for percutaneous mitral valvuloplasty. It consists of the following four elements, each one being graded from 1 to 4:

- 1) Valve thickness (only tips are thick **vs.** the whole valve is thickened)
- 2) Valve mobility (only leaflet tips are immobile **vs.** tips and body **vs.** tips, body, and base are immobile)
- 3) Valve calcification (spots of calcium **vs.** the whole leaflet is calcified)
- 4) Chordal thickening and calcification (thickening only underneath the leaflets **vs.** thickening extends towards the papillary muscles).

A score ≤ 8 makes the valve appropriate for commissurotomy.
 An additional feature that determines suitability for commissurotomy is the presence of calcium at the commissures. Commissural fusion is present in MS, but commissural calcium is only seen at a later stage and precludes successful commissurotomy, even if the Wilkins score is low.

Echo scores:

| Table 11-3: Assessment of mitral valve anatomy according to the Wilkins score: | | | | |
|--|----------|------------|---------------|------------------------|
| Grade | Mobility | Thickening | Calcification | Subvalvular thickening |

| | | | | |
|---|---|--|---|---|
| 1 | Highly mobile valve with only leaflet tips restricted | Leaflets near normal in thickness (4-5 mm) | A single area of increased echo brightness | Minimal thickening just below the mitral leaflets. |
| 2 | Leaflet mid and base portions have normal mobility | Mid leaflets normal, considerable thickening of margins (5-8 mm) | Scattered areas of brightness confined to leaflet margins | Thickening of chordal structures extending to one third of the chordal length |
| 3 | Valve continues to move forward in diastole, mainly from the base | Thickening extending through the entire leaflet (5-8mm) | Brightness extending into the mid portions of the leaflets. | Thickening extends to distal third of the chords. |
| 4 | No or minimal forward movement of the leaflet in diastole | Considerable thickening of all leaflet tissue (> 8-10mm) | Extensive brightness throughout much of the leaflet tissue | Extensive thickening and shortening of all chordal structures extending down to the papillary muscles |

The total score is the sum of the four items and ranges between 4 and 16

- **Score ≤ 8:** correlates with good results with PMC.
- **Score 9-12:** does not preclude PMc in selected cases.
- **Score > 12:** associated with poor results after PMC.

| Table 11-4: Assessment of mitral valve anatomy according to the cormier score: | |
|--|---|
| Echo group | Mitral valve anatomy |
| Group 1 | Pliable non calcified anterior mitral leaflet and mild subvalvular disease (i.e thin chordae ≥ 10 mm long) |
| Group 2 | Pliable non calcified anterior mitral leaflet and severe subvalvular disease (i.e thickened chordae < 10 mm long) |

Group 3

Calcification of mitral valve of any extent, assessed by fluoroscopy, whatever the state of subvalvular apparatus

Table 11-5: Echo score “Revisited” for immediate outcome prediction after PMC:

| Echocardiographic variables | Points for score (0-11) |
|---|--------------------------------|
| <i>Mitral valve area $\leq 1 \text{ cm}^2$</i> | 2 |
| <i>Maximum leaflet displacement $\leq 12 \text{ mm}$</i> | 3 |
| <i>Commissural area ratio ≥ 1.25</i> | 3 |
| <i>Subvalvular involvement</i> | 3 |

Three risk groups were defined:

- **Low risk (score of 0–3):** suboptimal PMC results of 16.9%.
- **Intermediate (score of 5):** suboptimal PMC results of 56.3%.
- **High (score of 6–11):** suboptimal PMC results of 73.8%.

▪ **Transesophageal Echocardiography:**

In general, TEE does not offer additional information in regard to the severity and morphology of MS (Wilkins score). The apical TTE views “look” directly into the subvalvular apparatus and allow estimation of the subvalvular thickening better than TEE, which “looks” at the mitral valve through the enlarged LA.

TEE should be performed:

1. Before PMC: to exclude LA thrombus and assess severity of MR.
2. After an embolic episode.

▪ **Catheterization:**

- Simultaneous LA-LV pressures should be obtained directly through a trans-septal puncture.

- Typically in severe MS, LV and LA pressures do not equalize at the end of diastole (diastasis is not reached ⁽¹⁾), even when the heart rate is controlled at 60-75 bpm. In fact, the lack of diastasis at a heart rate < 75 bpm or a pause of 1 second implies severe MS. Also, a large LA A wave with a discrepantly absent LV A wave suggests MS (LV underfilling).
- When MVA is 1-1.5 cm² but the heart rate is slow (≤ 60 bpm) and the cardiac output is low, diastasis may be reached at the end of diastole and the gradient may decline to 5 mmHg. Conversely, tachycardia may convert a mild MS gradient into a severe MS gradient with no diastasis.

In contrast to AS, the gradient of MS increases during tachycardia (short diastole) and decreases during long R-R cycles.

▪ **Stress testing and other maneuvers for MS ⁽²⁾:**

Resting transmitral gradient may not reflect the true severity of MS. As expressed in Gorlin's equation, for the same mitral valve area, the transmitral gradient is directly proportional to the square of the flow across the valve ($MVA \propto \text{transmitral flow}/\sqrt{\text{transmitral gradient}}$).

- Stress testing is helpful in asymptomatic severe MS. An exertional increase of systolic PA pressure to > 60 mmHg or a severe increase in transmitral gradient signifies that the patient is likely limited functionally and will benefit from an intervention to avoid the consequences of prolonged pulmonary hypertension.
- Stress testing is useful in symptomatic patients with mild/moderate MS, after ruling out tachycardia or high-output state, and helps sort out whether their symptoms are due to MS or LV failure.
 - In LV failure, both PCWP and LV diastolic pressure increases while the gradient remains unchanged.
 - In MS, PCWP and transmitral gradient increases while LV diastolic pressure remains unchanged.

MS is clinically significant and would likely benefit from an intervention if:

(1) During the mid portion of diastole (diastasis), the pressure in the LA and LV equilibrates, and mitral flow nearly ceases. Late in diastole, atrial contraction increases the atrial pressure, producing a second LA-to-LV pressure gradient that again propels blood into the LV.

(2) Note that, similarly to exercise, the heavy use of vasodilators increases cardiac output and the mitral gradient. Also, passive leg raising increases venous return and the mitral gradient. Dobutamine may also be used.

Mean transmitral gradient increases to > 15 mmHg; or Systolic PA pressure increases to > 60 mmHg or PCWP increases to > 25 mmHg without a significant increase in LVEDP.

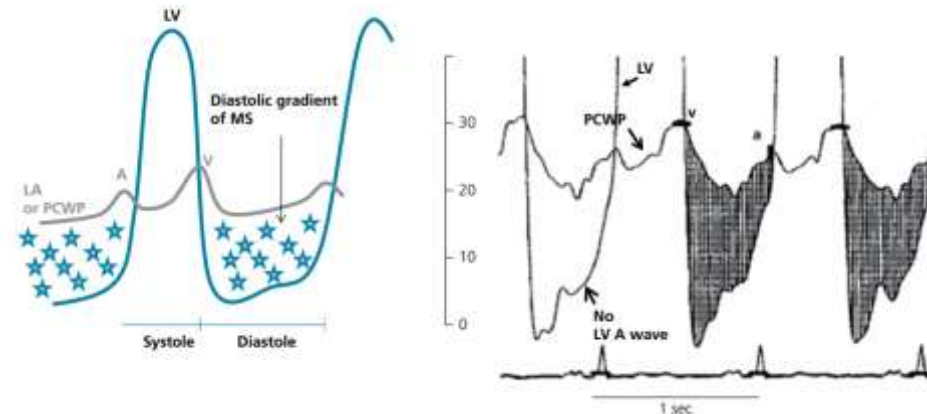


Figure 11-2: Two examples of mitral stenosis with a diastolic pressure gradient between PCWP and LV at a heart rate of 60 bpm (dark filled areas). Due to phase delay, the tracing of PCWP has been shifted to the left so that the *peak of the V wave almost intersects the LV downslope*. There is no LA-LV diastasis, i.e., LA pressure remains higher than LV pressure throughout diastole, signifying severe MS. *LA A wave is pronounced but LV A wave is reduced because of ventricular underfilling.* With more severe MS, the LA pressure tracing is higher and the intersection between V wave and LV occurs earlier; *this translates into an opening snap that is closer to S2.* **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

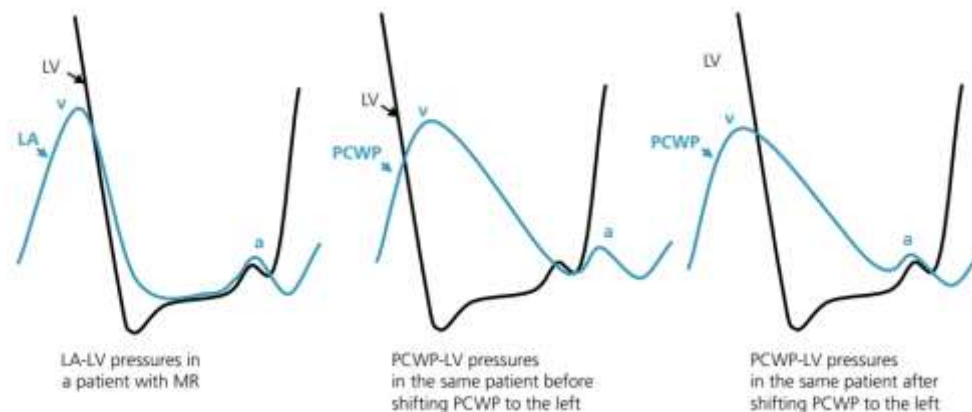


Figure 11-3: False impression of MS resulting from the use of PCWP as a surrogate for LA pressure in a patient with severe MR. When LA-LV pressures are simultaneously recorded, an early diastolic gradient is seen between LA and LV and is quickly followed by diastasis. However, when PCWP-LV pressure recording is performed, the damped and prolonged Y descent creates the impression of a large pressure gradient and a lack of diastasis, even when PCWP is appropriately shifted to the left, thus creating the impression of MS. Also, in comparison to patients without concomitant MR, patients with combined MS and MR are more likely to have their transmitral gradient overestimated with the use of PCWP. Note that LV A wave is still present and prominent, arguing against severe MS. **Source:** Hanna EB, Glancy DL. Practical Cardiovascular Hemodynamics. New York, NY: Demos Medical, 2012, p. 101.

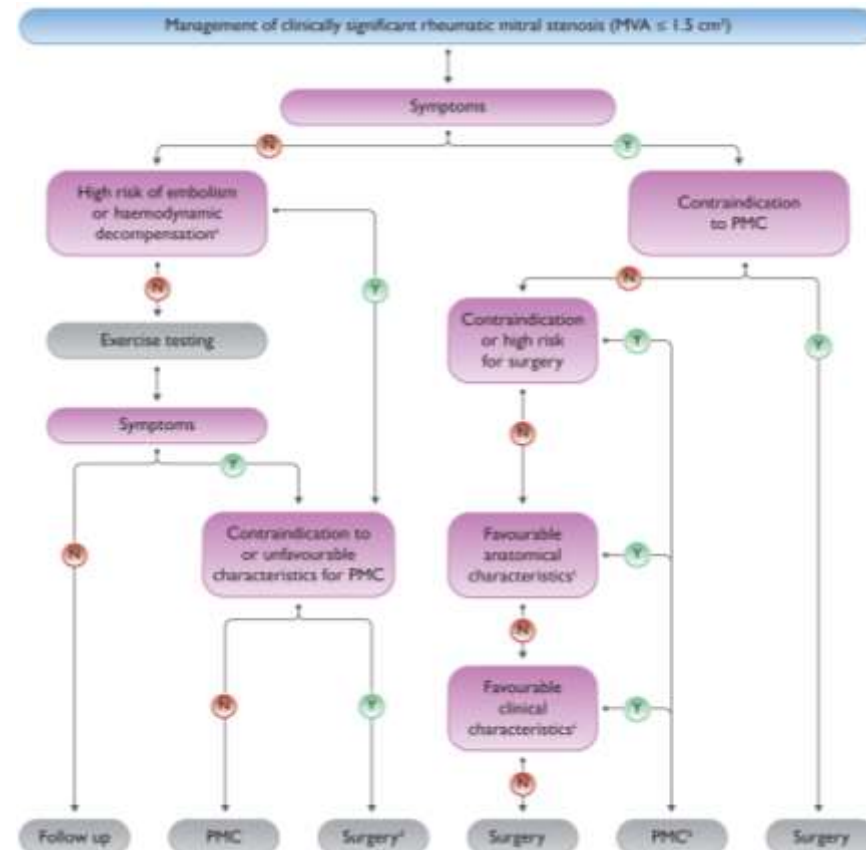


Figure 11-4: Management of clinically significant rheumatic mitral stenosis (MVA ≤ 1.5 cm²). **A)** High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the LA, new-onset AF. **High-risk of haemodynamic decompensation:** systolic pulmonary pressure > 50 mmHg at rest, need for major NCS, desire for pregnancy. **B)** Surgical commissurotomy may be considered by experienced surgical teams in patients with contraindications to PMC. **C)** See recommendations on indications for PMC and mitral valve surgery in clinically significant mitral stenosis. **D)** Surgery if symptoms occur for a low level of exercise and operative risk is low. Source: 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

▪ **Intervention therapy:**

Table 11-6: ESC Recommendations on indications for percutaneous mitral commissurotomy and mitral valve surgery in clinically significant mitral stenosis (valve area $\leq 1.5 \text{ cm}^2$):

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>PMC is recommended in symptomatic patients without unfavourable characteristics for PMC⁽¹⁾.</i> | I | B |
| <i>PMC is recommended in any symptomatic patients with a contraindication or a high risk for surgery.</i> | I | C |
| <i>Mitral valve surgery is recommended in symptomatic patients who are not suitable for PMC in the absence of futility.</i> | I | C |
| <i>PMC should be considered as initial treatment in symptomatic patients with suboptimal anatomy but no unfavourable clinical characteristics for PMC.</i> | IIa | C |
| <i>PMC should be considered in asymptomatic patients without unfavourable clinical and anatomical characteristics for PMC and:</i> <ul style="list-style-type: none"> <i>High thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the LA, new-onset or paroxysmal AF), and/or</i> <i>High risk of haemodynamic decompensation (systolic pulmonary pressure >50mmHg at rest, need for major NCS, desire for pregnancy).</i> | IIa | C |

(1) Unfavourable characteristics for PMC can be defined by the presence of several of the following characteristics.

Clinical characteristics: old age, history of commissurotomy, NYHA class IV, permanent AF, and severe pulmonary hypertension.

Anatomical characteristics: echocardiographic score > 8, Cormier score 3 (calcification of mitral valve of any extent as assessed by fluoroscopy), very small MVA, severe tricuspid regurgitation.

Percutaneous Mitral Commissurotomy (or percutaneous mitral balloon valvotomy [PMBV]): When feasible, PMC is the therapy of choice for MS. A successful PMC is defined as a post-PMBV valvular area $\geq 1.5 \text{ cm}^2$ with \leq moderate (2+) MR.

- **Complications:**

- Mortality= 1-2%
- Stroke ~1%
- Risk of severe MR ~2-5% (moderate MR ~15%).
- Restenosis occurs at a rate of ~20% at 10 years.
- ~25% of patients require MV replacement within 5 years, whether for restenosis, progression of a suboptimal result, or progression of MR.

- **Contraindications for PMC:**

- MVA $> 1.5 \text{ cm}^2$
- Left atrial thrombus, if thrombus is present, give 1-3 months of anticoagulation then reassess and attempt PMC if the thrombus resolves.
- More than mild MR
- Severe or bicommissural calcification
- Absence of commissural fusion
- Severe concomitant aortic valve disease, or severe combined TS and TR requiring surgery.
- Concomitant CAD requiring bypass surgery.

- **Unfavourable characteristics for PMC:**

- **Clinical characteristics:** Old age, History of commissurotomy, NYHA class IV, Permanent AF, and Severe pulmonary hypertension.

- **Anatomical characteristics:** Wilkins score > 8 ⁽¹⁾, Cormier score 3 (calcification of mitral valve of any extent as assessed by fluoroscopy), Very small mitral valve area, and Severe tricuspid regurgitation.
- **Medical therapy:** Medical therapy is not usually indicated as a standalone therapy, as even patients with class II symptoms have impaired long-term outcomes without mechanical relief of MS.
 - Diuretics, beta-blockers, or heart rate-regulating CCBs can transiently improve symptoms. β -Blockers increase diastolic time, allowing more time for LA emptying. A heart rate of 60 bpm should be targeted.
 - Standalone medical therapy may be used in select patients with class II symptoms:
 - Patients who improve after PMBV but have residual symptoms.
 - Patients with mild/moderate MS that is symptomatic because of hemodynamic disturbances (tachycardia, high cardiac output).
 - Sedentary, elderly patients with mild symptoms on exertion. This includes senile MS.
 - Anticoagulation (with a target INR 2 - 3) is indicated in:
 - Patients with either new-onset or paroxysmal AF. The yearly risk of stroke with the AF-MS combination is 10-15% per year, implying a critical role of warfarin therapy.
 - Patients in sinus rhythm, with a history of systemic embolism or a thrombus is present in the LA
 - When TOE shows dense spontaneous echocardiographic contrast or an enlarged LA (M-mode diameter > 50 mm or LA volume > 60 mL/m²).

N.B:

(1) *Valvotomy works by splitting the fused commissures. Unlike AS, early MS mainly consists of a commissural fusion that is not calcified. Tearing this fusion opens the mitral orifice, and thus balloon valvotomy is effective in treating early MS.*

Once the fibrosis and the immobility extend to the body of the leaflets or the subvalvular apparatus, or once calcium develops, valvotomy becomes less effective and risks tearing the stiff unyielding valve or the subvalvular apparatus in the process of dilating the orifice. Also, the balloon may get stuck in the thick subvalvular apparatus and tear it upon inflation. This is how Wilkins score and commissural calcium predict outcomes with PMC.

The reduction of PCWP and transmitral gradient with a longer diastole makes β -blocker therapy important in decompensated MS with pulmonary edema. A similar benefit of β -blockade is seen when pulmonary edema is related to HOCM. No other case of decompensated left heart failure, whether systolic or diastolic, is acutely served by β -blockers.

Follow-up:

Asymptomatic patients with clinically significant mitral stenosis should be followed up **yearly** by clinical and echocardiographic examinations; and at longer intervals (2-3 years) in case of moderate stenosis.

Follow-up of patients after successful PMC is similar to that of asymptomatic patients and should be more frequent if asymptomatic restenosis occurs.

Special patient populations:

AF and MS

- β -blockers and/or digoxin are used for rate control. Rhythm control may be attempted after a new onset of AF, but repeated DC cardioversions should be avoided in light of the associated stroke risk and the fact that, over time, rhythm control is difficult to achieve in MS.
- Neither cardioversion nor catheter pulmonary vein isolation are indicated before intervention in patients with significant mitral stenosis, as they do not durably restore sinus rhythm.
- When surgery is performed for MS or MR associated with AF, maze procedure (bilateral ablation lines that include the pulmonary veins, the venae cavae, and the valvular annuli) may be performed and are associated with a high success in maintaining sinus rhythm (up to 80%), even in patients with LA enlargement.
- Amiodarone is most effective in maintaining the sinus rhythm after cardioversion.

Moderate MS (MVA 1.5-2 cm²)

- Symptomatic patients with *moderate gradient at rest* need to be assessed with stress testing.
A severe increase in transmitral gradient without a significant change in LVEDP implies that MS is hemodynamically significant and may benefit from PMBV.
- Patients with moderate anatomic MS who have a *severe gradient at rest* need to be invasively assessed and managed as following:
 - If there is hemodynamic disturbances (tachycardia, high-output state e.g vasodilator therapy), treat it.
 - In the absence of those hemodynamic disturbances, moderate MS may be the cause of the severe gradient and the severe pulmonary hypertension and may warrant PMBV ⁽¹⁾.

Degenerative MS with mitral annular calcification

- Usually, these patients are elderly and may have significant comorbidities including disease of other valves. Severe MAC may result in mitral stenosis (more frequently) or mitral regurgitation, or both.
- In patients with degenerative mitral stenosis and MAC, the echocardiographic evaluation of the disease severity is difficult, and the usual parameters lack validation. If an intervention is planned, echocardiography is used for initial evaluation and CCT is necessary to assess the degree and location of calcification and to evaluate the feasibility of an intervention.
- **Indications for intervention:**
 - Treatment options, including transcatheter and surgical approaches, are high-risk procedures and evidence from randomized trials is lacking. As there is no commissural fusion, degenerative mitral stenosis is not amenable to PMC.
 - In symptomatic inoperable patients with suitable anatomy, preliminary experience showed that transcatheter mitral valve implantation (in mitral position, using an inverted balloon-expandable TAVI prosthesis), is feasible in selected patients with severe mitral stenosis, when performed by experienced operators after careful preplanning using multimodality imaging.

(1) MVA of 1.6 cm² may imply severe MS when indexed for body size.

Mitral regurgitation

Mitral regurgitation is the second-most frequent indication for valve surgery in Europe.

MR could be the cause of LV dysfunction (intrinsic MR) or, much more commonly, the result of it (functional or secondary MR). It is essential to distinguish primary from secondary mitral regurgitation, as these two conditions are treated differently (intrinsic MR requires valvular repair, whereas the first-line therapy of functional MR is treatment of the underlying LV dysfunction).

Mechanisms of mitral regurgitation:

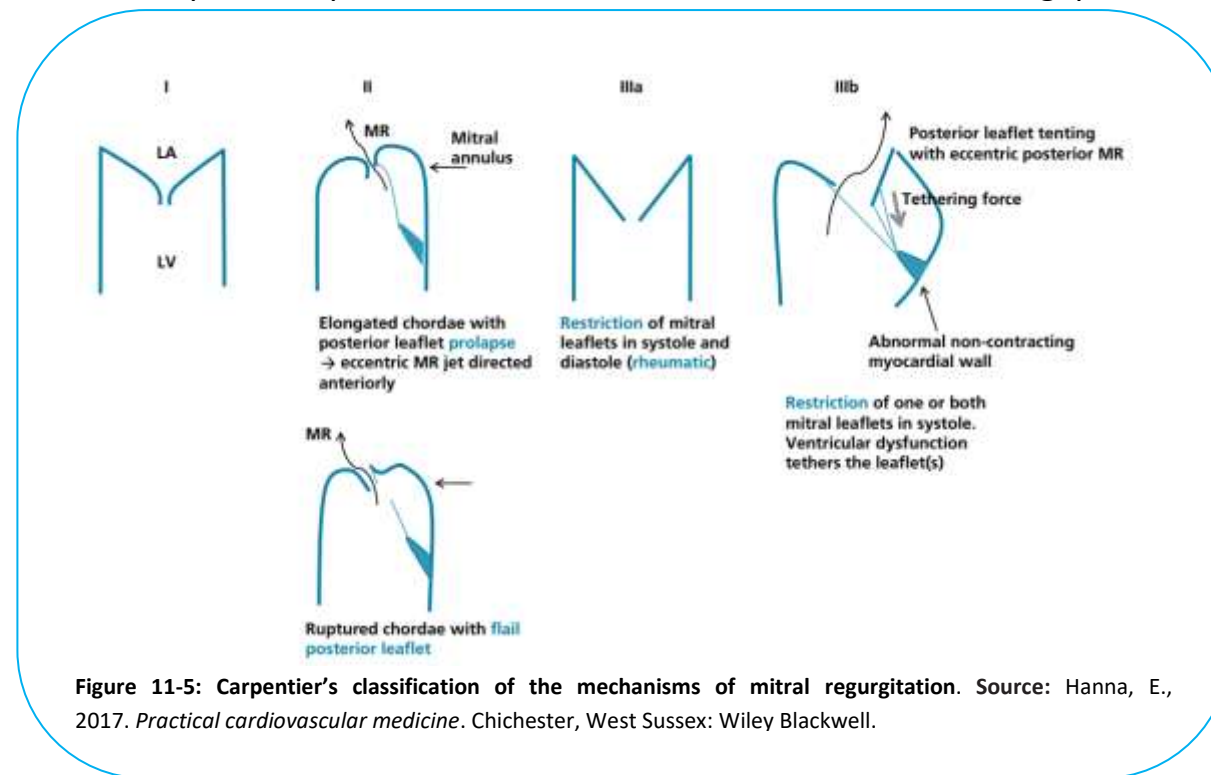
There are four major mechanisms of mitral regurgitation (Carpentier's classification):

- **Type I:** Normal leaflet motion.
MR occurs despite normal leaflet motion and leaflet tip position. Type I MR may occur with leaflet **tear(s)** secondary to endocarditis or blunt trauma.
- **Type II:** Excessive leaflet motion
Prolapse of one or both leaflets, i.e., the billowing body of the leaflet is > 2mm above the annular plane (the free edge of the leaflet is at the annular plane or above it).
If, in addition to the prolapse of the leaflet body, the free edge is overriding the other leaflet and turned towards the LA rather than the LV, the leaflet is called a flail leaflet; this is usually secondary to chordal rupture (a piece of chordae is usually seen flopping in the LA). Type II MR may result from mitral valve prolapse, chordal rupture (from mitral valve prolapse, endocarditis, trauma), or papillary muscle rupture (MI, trauma).
- **Type IIIa:** Restricted leaflet motion during diastole and systole (i.e restricted opening)
The leaflets and chordae are thickened, retracted, and shortened, with chordal fusion (**rheumatic** or rheumatic-like process).
The mitral motion is restricted in both systole and diastole, potentially leading to both MS and MR.
- **Type IIIb:** Restricted leaflet motion during systole (i.e restricted closure)

Functional MR. A localized, inferior ventricular dysfunction pulls the papillary muscle(s) and chorda(e) posterolaterally, predominantly restricting the motion of the posterior leaflet (leaflet tethering). In severe global LV dysfunction, the ventricular geometry changes from an ellipse to a sphere, which pulls both leaflets posterolaterally and apically, restricting their closure.

Three additional mechanisms contribute to MR:

- Annular dilatation, which reduces leaflet coaptation.
- Reduced LV systolic pressure, which reduces the mitral valve closing force and sometimes leads to MR even when tethering is mild.
- Papillary muscle dyssynchrony (e.g., in patients with LBBB or RV pacing): one papillary muscle contracts while the other is relaxed; therefore, one leaflet is pushed up while the other is still down, which creates a gap between the two leaflets.



Causes of mitral regurgitation:

- **Acute MR:** In acute MR, EF increases to allow an increase in total stroke volume, the forward stroke volume remaining, however, low. The patient is in shock with pulmonary edema, LA pressure is severely increased, yet the intrinsic LV function is normal, and the LV diastolic pressure may be normal ⁽¹⁾.

Causes of acute MR:

- Mitral valve endocarditis: the vegetations may interfere with proper leaflet coaptation or may destroy and perforate the leaflet(s) or chorda(e).
- Papillary muscle rupture or acute functional MR occurring in the context of an acute MI.
- Chordae tendinae rupture. Causes: idiopathic, mitral valve prolapse, endocarditis, trauma.
- Acute functional MR secondary to an acute ventricular process (MI, myocarditis).
- **Primary MR:** [Primary lesion of one or more components of the mitral valve apparatus]
- **Rheumatic fever:** Rheumatic fever leads to scarring and constriction of the leaflets and the subvalvular apparatus, restricting mitral valve closure (→ MR) and opening (→ MS). A predominant or isolated MR may be seen with rheumatic heart disease. It is the most common cause of MR in low-income countries.
- **Mitral Valve Prolapse (MVP):**
 - MVP is defined as One or two cusps prolapse > 2 mm into the LA above the annulus level, in the long-axis view ⁽²⁾. It is the most frequent cause of MR in western countries.
 - There are two forms of MVP:
 1. Fibroelastic deficiency (common in patients > 50 years), wherein the prolapsed leaflet(s) are **thin**;
 2. Barlow disease or classic MVP (common in women < 50 years), wherein the prolapsed leaflets and chordae are **thick**.

(1) In acute MR, LVEF is increased rather than decreased. Acute HF with low EF and severe MR usually implies functional rather than primary MR.

(2) A prolapse seen in the apical four-chamber view is less specific and should not be used to define MVP.

- MVP occurs in 1-2% of the population with a familial trend. Female-to-male ratio= 2:1.
- MVP most commonly involves the posterior leaflet, especially the posterior cusp P2. When confined to a single cusp, the prolapsed or the flail leaflet may be missed by TTE. MR is often very eccentric, hugging the LA wall and directed opposite to the prolapsed leaflet.
- MVP may be associated with tricuspid prolapse (in ~40%) and aortic valve prolapse (in ~10%).
- 15% of MVP cases progress to severe MR at a mean follow-up duration of 15 years.
- MVP, regardless of its severity, can be associated with autonomic dysfunction (e.g., orthostatic intolerance) and atypical complaints (chest pain, fatigue, palpitations).
- Complications in serious MVP subgroup: **(1)** severe MR; **(2)** endocarditis; **(3)** VT/sudden death.
- **Secondary (Functional) MR:**

In secondary mitral regurgitation, the valve leaflets and chordae are structurally normal and mitral regurgitation results from an imbalance between closing and tethering forces on the valve secondary to alterations in LV geometry (Ventricular FMR) or atrial dilatation (Atrial FMR) or both.
- **In ventricular FMR:** MR may be secondary to ischemic or non-ischemic global LV dysfunction, with an MR jet that is central or posteriorly directed. Ischemic MR is not a valvular problem; it is a problem of segmental ventricular distortion and, to a lesser extent, increased ventricular sphericity. A posterior change in LV geometry tethers the posterior papillary muscle posterolaterally; subsequently, both leaflets are tethered, predominantly the posterior leaflet.
- **In atrial FMR:** MR occurs secondary to annular dilatation in patients with atrial dysfunction (e.g., chronic AF or atrial myopathy) or in patients with HFpEF.
- **Other causes of MR:**
 - Healed endocarditis with progressive scarring and retraction of the mitral leaflet(s) may lead to late MR.
 - Systolic anterior motion of the anterior leaflet and chordae in HOCM.

- Severe posterior mitral annular calcifications (MAC). MAC may immobilize the basal portion of both mitral leaflets, preventing their normal excursion in diastole (→ MS) and coaptation in systole (→ MR). Also, the mitral annulus loses its expansile function (→ MS) and contractile function (→ MR).

- **Causes of transient severe MR:**

- Acute, transient LV dysfunction: Any process leading to acute ventricular dysfunction may be associated with acute leaflet tethering and acute functional MR. Examples include acute ischemic events, but also takotsubo cardiomyopathy, myocarditis, and postpartum cardiomyopathy.
- Dynamic ischemic/functional MR: functional MR (due to chronic LV dysfunction) may worsen with changes in LV volume and geometry. The acute increase in preload and/or afterload (e.g., due to HF decompensation, exercise, prolonged supine position, Hypertension) worsens a mild ischemic/functional MR. These changes in loading conditions do not affect the severity of an organic MR, yet they do affect the regurgitant volume, the LA pressure, and the degree of pulmonary edema.

The concept of dynamic MR is an important concept, as it may explain exertional or nocturnal symptoms and pulmonary edema in patients with mild ischemic MR at rest. In this case, MR, LA pressure, and PA pressure increase during exercise or during sleep with the increase in venous return. This is proven by stress echocardiography, wherein MR severity and PA pressure increase without any ECG or echocardiographic signs of ischemia.

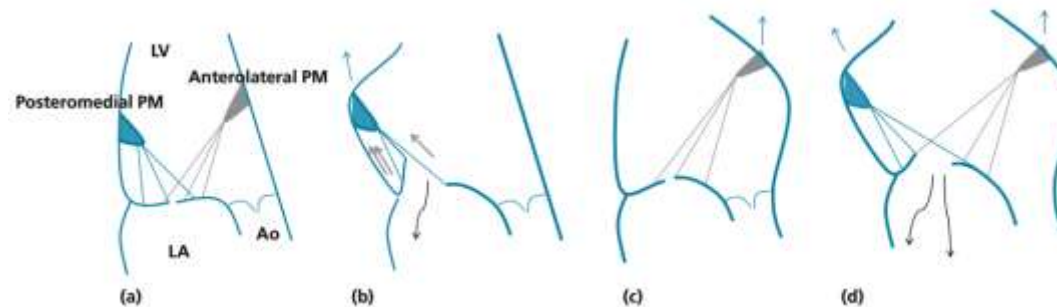


Figure 11-6: Illustration of ischemic MR on longitudinal views. (A) Normal valvular anatomy. Both papillary muscles (PM) provide chordae to both mitral leaflets. **(B) Inferior akinesis with posterolateral displacement of the posterior papillary muscle (PM).** This leads to major restriction of the posterior leaflet and minor restriction of the anterior leaflet. **(C) Anterior akinesis,** by itself, does not lead to major restriction of any leaflet as it pulls the leaflets axially rather than sideways. **(D) Anterior MI with global remodeling and global LV dilatation pulls both the anterior and posterior papillary muscles apically and posterolaterally.** Both leaflets are tethered, and the jet may be central or predominantly posterior (if the posterior leaflet is more tethered than the anterior leaflet). Note that ischemic MR cannot be anteriorly directed (it is either central or posterior). **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

N.B:

- ☞ An eccentric, anteriorly directed jet can't be seen with ischemic MR.
- ☞ In the setting of inferior MI, acute ischemic MR related to leaflet restriction should be distinguished from papillary muscle rupture (the leaflet is restricted in the former vs. prolapsed in the latter).
- ☞ Note that annular dilatation, by itself, does not lead to functional MR. The ratio of leaflet area to annular surface area being normally > 2:1, very severe annular dilatation would be required to cause inadequate mitral coaptation. Annular dilatation is, however, a contributing factor in ischemic MR. In addition, the annulus normally has a contractile function in systole. The loss of annular contraction reduces the coaptation of the tented leaflet and contributes to MR.

- ☞ Avoid assessing ischemic MR intraoperatively. The unloading conditions of anesthesia convert the dynamic, severe ischemic MR into mild MR.

Assessment of MR:

▪ Transthoracic Echocardiography:

| Table 11-7: Severe mitral regurgitation criteria based on 2D echocardiography: | | |
|--|---|---|
| | Primary mitral regurgitation | Secondary mitral regurgitation |
| Qualitative: | | |
| Mitral valve morphology | Flail leaflet, ruptured papillary muscle, severe retraction, large perforation | Normal leaflets but with severe tenting, poor leaflet coaptation |
| Colour flow jet area | Large central jet (> 50% of LA) or eccentric wall impinging jet of variable size. | |
| Flow convergence | Large throughout systole | |
| Continuous wave Doppler jet | Holosystolic/dense/triangular | |
| Semiquantitative: | | |
| Vena contracta width | ≥ 7 (≥ 8 mm for biplane) | |
| Pulmonary vein flow | Systolic flow reversal | |
| Mitral inflow | E-wave dominant (> 1.2 m/s) | |
| TVI _{mitral} /TVI _{aortic} | > 1.4 | |
| Quantitative: | | |
| EROA (mm ²) | ≥ 40 mm ² | ≥ 40 mm ² (may be ≥ 30 mm ² if elliptical regurgitant orifice area) |

| | | |
|--|---|---|
| Regurgitant volume (mL/beat) | $\geq 60 \text{ mL}$ | $\geq 60 \text{ mL}$ (may be $\geq 45 \text{ mL}$ if low flow conditions) |
| Regurgitant fraction (%) | $\geq 50\%$ | |
| Structural: | | |
| Left ventricle | <i>Dilated (ESD $\geq 40 \text{ mm}$)</i> | <i>Dilated</i> |
| Left atrium | <i>Dilated (diameter $\geq 55 \text{ mm}$ or volume $\geq 60 \text{ mL/m}^2$)</i> | <i>Dilated</i> |

- **Transesophageal Echocardiography:**

TEE is performed if the severity or the cause of MR is unclear by TTE. It is also valuable in assessing which cusp(s) is involved and whether repair is feasible. Three-dimensional TEE provides an 'en face' view of the mitral leaflets resembling the surgical inspection of the valve, thereby facilitating Heart Team discussion. In addition, 3D echocardiography has shown better agreement with CMR in quantifying the regurgitant volume than 2D echocardiography, particularly in eccentric, multiple and late-systolic regurgitant jets.

- **Cardiac MRI:**

When various echocardiographic parameters used to grade MR are inconsistent, CMR is a valid alternative to quantify the regurgitant volume and is the standard to quantify LV and LA volumes.

- **Exercise echocardiography** permits evaluation of changes in mitral regurgitant volume and pulmonary pressures during peak exercise and is particularly helpful in patients with discordant symptoms and regurgitation grade at rest.

- **Left ventriculography:**

Left ventriculography is indicated if the echo data are inconclusive or when there is discrepancy between the echo data and the clinical findings. When properly done, ventriculography is highly accurate in MR grading, as it semi-quantitatively addresses the regurgitant volume rather than velocity.

In severe MR, LA entirely fills with contrast, as intensely as LV (= 3+ MR), or more intensely than LV, sometimes with pulmonary venous filling (= 4+ MR).

▪ **Right heart catheterization:**

Right heart catheterization may be performed as an adjunct to left ventriculography when the severity of MR is unclear. The finding of an ample V wave that exceeds 45 mmHg or is twice the mean PCWP suggests severe MR. However, the V wave may not be that ample in severe but compensated MR. An ample V wave may also be seen with decompensated HF, even without MR.

In addition, the invasive measurement of PA pressure and PCWP at rest and with stress is valuable in addressing the surgical indication when MR is severe, but symptoms are mild and non-specific. An elevated PCWP implies that MR is likely functionally limiting, even if the patient denies any symptom.

N.B:

- ☞ In asymptomatic patients, the significant increase of pulmonary artery pressure with exercise (> 60 mmHg) has been reported to be of prognostic value.
- ☞ In asymptomatic patients with severe PMR and non-dilated LV and LA, low BNP values are associated with low mortality and can be useful during follow-up.
- ☞ Acute severe MR may look mild on TTE. The increased LA pressure reduces the LV-LA pressure gradient and the MR velocity, which may reduce the color signal and turbulence; also, acute MR may be eccentric. Thus, if a patient with a questionable MR severity and a normal or hyperdynamic LV has severe pulmonary edema, think of severe MR and perform TEE or left ventriculography.

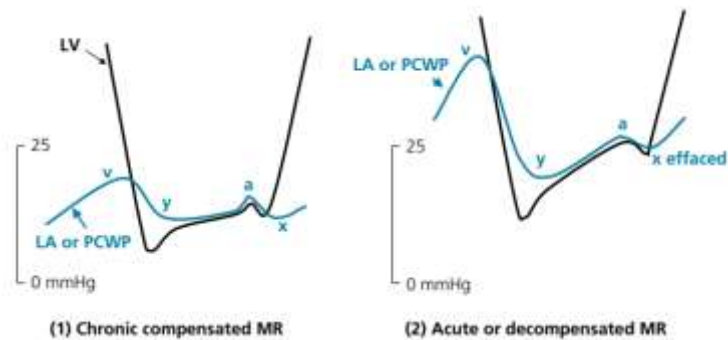


Figure 11-7: Difference in V wave and LV diastolic pressure between (1) chronic compensated MR and (2) acute or decompensated MR. In decompensated MR, V wave gets larger, Y descent gets deeper, while X descent gets shallower. LA pressure may switch from (1) to (2) with simple maneuvers: handgrip (\uparrow afterload), small volume loading, exercise. LA pressure may switch from (2) to (1) with sedation, acute hypertension control, or nitroprusside infusion (\downarrow preload and afterload). **Source:** Hanna EB, Glancy DL. Practical Cardiovascular Hemodynamics. New York, NY: Demos Medical, 2012, p. 112.

Natural history of organic MR:

- Even among asymptomatic patients with normal LV function, severe MR leads to symptoms or LV dysfunction in 100% of patients at ~5 years. Asymptomatic severe MR is associated with the following yearly risks: 0.8% sudden death, 5-6% cardiac death, 10% combined cardiac death, HF, or AF, and ~20% death or requirement for valvular surgery (fast progression).
- Once symptomatic, the mean survival of severe MR is ~3 years without surgical correction.

Management:

- Acute severe MR related to acute MI:

- In case of papillary muscle rupture, perform emergent valvular surgery + CABG. Place IABP preoperatively and consider IV vasodilators (nitroprusside) if blood pressure allows, as in all cases of acute severe MR. MV replacement is often performed, as it is more expeditious than repair.
- In case of acute mitral leaflet tethering, treat the patient medically with vasodilators and place IABP for temporary support. It is expected that leaflet tethering will improve once the function of the reperfused territory improves. Surgery should be considered as a second-line therapy for those patients who do not improve with medical therapy.
- **Primary mitral regurgitation:**
In primary mitral regurgitation, one or several components of the mitral valve apparatus are directly affected. The most frequent aetiology is degenerative (prolapse, flail leaflet).

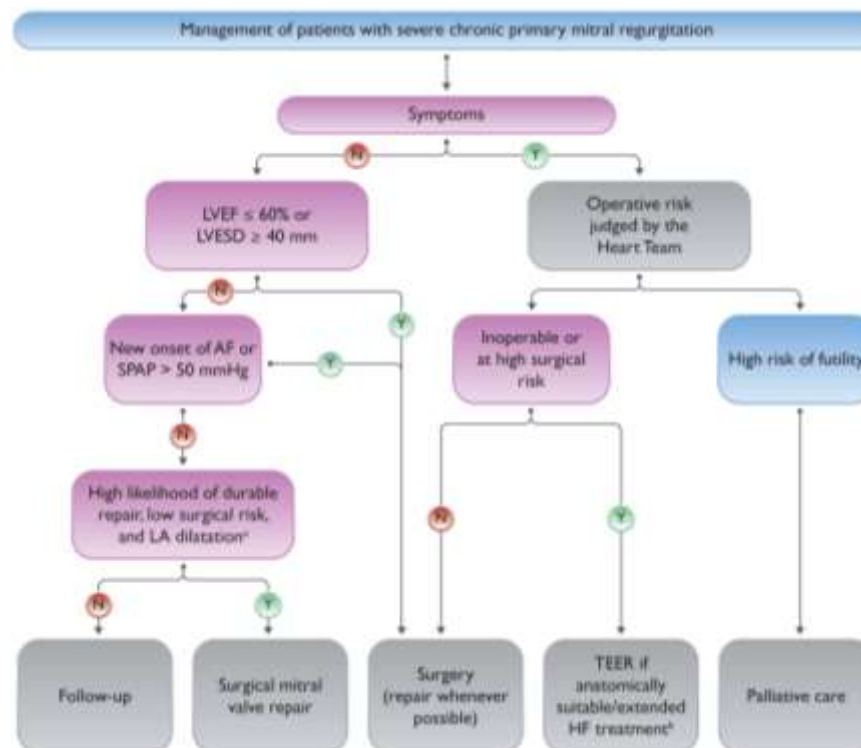


Figure 11-8: Management of patients with severe chronic primary MR. A) LA dilatation: volume index ≥ 60 mL/m² or diameter ≥ 55 mm at sinus rhythm. **B)** Extended HF treatment includes the following: CRT; LVAD; heart transplantation. **Source:** 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

○ Indication for intervention:

Table 11-8: ESC Recommendations on indications for intervention in severe primary MR:

Recommendations

Class Level

| | | |
|---|-----|---|
| Mitral valve repair is the recommended surgical technique when the results are expected to be durable. | I | B |
| <p>Surgery is recommended in:</p> <ul style="list-style-type: none"> - symptomatic patients who are operable and not high risk - asymptomatic patients with LV dysfunction (LVESD \geq 40 mm and/or LVEF \leq 60%). | I | B |
| Surgery should be considered in asymptomatic patients with preserved LV function (LVESD < 40 mm and LVEF > 60%) and AF secondary to mitral regurgitation or pulmonary hypertension ⁽¹⁾ (SPAP at rest > 50 mmHg). | IIa | B |
| Surgical mitral valve repair should be considered in low-risk asymptomatic patients with LVEF > 60%, LVESD < 40 mm and significant LA dilatation (volume index \geq 60 mL/m ² or diameter \geq 55 mm) when performed in a Heart Valve Centre and a durable repair is likely. | IIa | B |
| TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team and for whom the procedure is not considered futile. | IIb | B |

- **Medical therapy:** with good ventricular function: there is no evidence to support the prophylactic use of vasodilators, including ACE inhibitors. Beta blockers and spironolactone (or eplerenone) should also be considered as appropriate. In patients with overt heart failure, medical treatment as per current heart failure guidelines applies.
- **Follow-up:**

(1) If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement.

- Asymptomatic patients with severe mitral regurgitation and LVEF > 60% should be followed clinically and by echocardiography **every 6 months**. Measurement of BNP levels, exercise echocardiography, Holter monitoring and CMR are useful complementary diagnostic and risk stratification tools.

In asymptomatic patients with severe PMR and progressive increase of LV size (LVESD approaching 40 mm) or decrease of LVEF on serial studies, surgical mitral valve repair should be discussed.

- Asymptomatic patients with moderate MR and preserved LV function can be followed on a **yearly** basis and echocardiography should be performed every 1-2 years.
- After intervention, serial follow-up focuses on evaluation of symptomatic status, presence of arrhythmic events, assessment of valve function, and recurrence of mitral regurgitation.
- After transcatheter mitral valve repair, the currently reported rates of residual moderate and severe mitral regurgitation (23-30%) would suggest that **yearly** echocardiogram is appropriate.

N.B:

☞ LV function may deteriorate after mitral surgery:

- This is partly related to damaging the subvalvular annular-chordal-papillary muscle continuity during mitral valve replacement, which leads to a change in the LV geometry (from elliptical to spherical) and the effectiveness of LV contraction.
- Closing the low-resistance leak increases afterload in the immediate postoperative period. This “afterload mismatch” contributes to early EF deterioration. This may even happen in ~25% of patients with baseline LV dysfunction and in < 10% of patients with normal EF. Yet, afterload mismatch is unlikely to affect long-term EF, as reducing MR also reduces LV volume and improves long-term EF (EF often returns to baseline before hospital discharge).

☞ Advantages of MV repair:

- MV repair preserves the subvalvular apparatus and the LV geometry ⁽¹⁾.
- MV repair protects from the LV deterioration that commonly occurs after MV replacement.
- Postoperative mortality after MV repair may be very low (< 1%) and approximates half the mortality of MV replacement.

(1) *Even if MV replacement is performed, the MV apparatus should be preserved and fixed to the annulus rather than resected to preserve the ventricular geometry.*

- MV repair does not necessitate chronic anticoagulation therapy.
 - MV repair is feasible in MVP, mainly posterior leaflet MVP, but also leaflet perforation secondary to endocarditis, when the annulus is not involved and tissue destruction is limited. MV repair is also recommended for anterior leaflet prolapse, albeit the success rate is lower. MV repair is least successful in rheumatic, calcified MR. MV repair may be more technically challenging than MV replacement and, in case of failure, requires longer pump time, which may not be tolerated in the sickest patients.
- ☞ *Immediately postoperatively, ~10% of patients undergoing MV repair for MVP develop significant SAM of the anterior leaflet with LVOT obstruction and significant MR. This MR may be misdiagnosed as failed repair. SAM is secondary to the anterior leaflet being “squeezed” down into the LV by the narrow annuloplasty ring and therefore touching the septum, particularly if the LV cavity is small and the anterior leaflet is long and redundant. Moreover, the increase in steepness of the mitro-aortic angle moves the leaflet coaptation line anteriorly towards the LVOT. SAM immediately improves with fluid administration and cessation of inotropic drugs.*

▪ **Secondary mitral regurgitation:**

• **Medical therapy:**

Optimal medical therapy in line with the guidelines for the management of heart failure should be the first and essential step in the management of all patients with SMR.

If symptoms persist after optimization of conventional heart failure therapy, options for mitral valve intervention should be evaluated before further deterioration of LV systolic function.

• **Indications for intervention:**

Table 11-9: ESC Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|---|-----|---|
| Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team. | I | B |
| Patients with concomitant coronary artery or other cardiac disease requiring treatment: | | |
| Valve surgery is recommended in patients undergoing CABG or other cardiac surgery. | I | B |
| In symptomatic patients, who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics ⁽¹⁾ , PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered. | IIa | C |
| Patients without concomitant coronary artery or other cardiac disease requiring treatment: | | |
| TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment ⁽²⁾ . | IIa | B |
| Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team. | IIb | C |
| In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant. | IIb | C |

(1) LVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise.

(2) According to COAPT-like profile, All the following should be fulfilled: (A) LVEF \geq 20% (B) LVEDD \leq 70 mm. (C) SPAP \leq 70 mmHg (D) Absence of severe RV dysfunction (TAPSE \geq 15 mm and/or RV s' \geq 8 cm/s) (E) Absence of severe TR (F) Absence of hemodynamic instability.

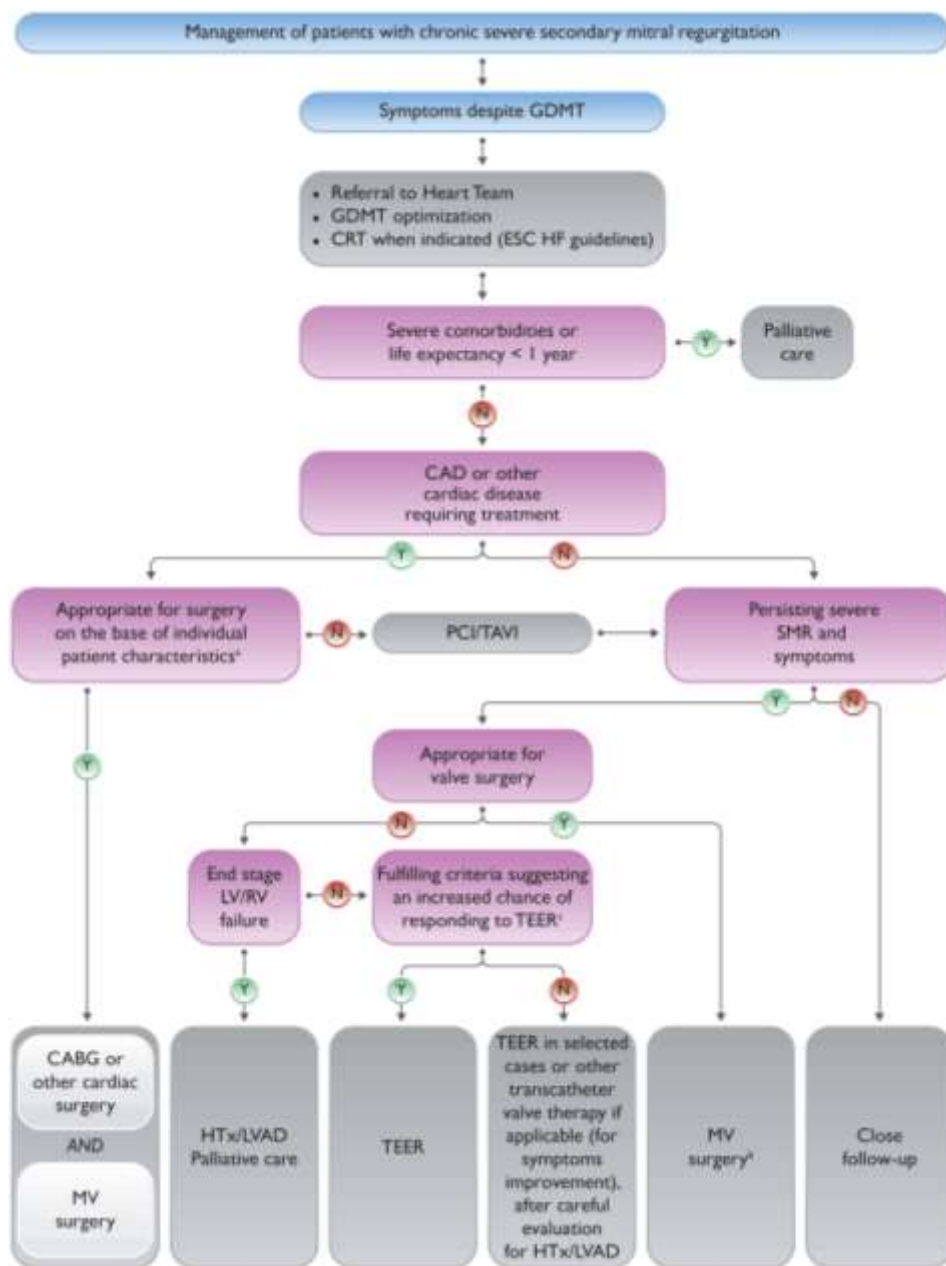


Figure 11-9: Management of patients with chronic severe secondary mitral regurgitation. A) LVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise. **B)** Particularly when concomitant tricuspid valve surgery is needed. **C) COAPT criteria:** All the following should be fulfilled: (i) LVEF $\geq 20\%$ (ii) LVEDD ≤ 70 mm. (iii) SPAP ≤ 70 mmHg (iv) Absence of severe RV dysfunction (TAPSE ≥ 15 mm and/or RV s' ≥ 8 cm/s) (v) Absence of severe TR (vi) Absence of hemodynamic instability. **Source:** 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

Aortic stenosis

Aortic stenosis is the most common primary valve disease leading to surgery or catheter intervention in Europe and North America, with a growing prevalence due to the ageing population.

Aetiology:

- **Age-related calcific degeneration** (most common cause):

It is related to endothelial valvular injury and has the same risk factors as atherosclerosis/CAD. Calcifications develop throughout the valve leaflets *rather than specifically over the commissures*.

Non-stenotic aortic valve sclerosis (thickening) precedes AS, is present in ~20 % of patients > 65 years, and progresses to some degree of AS in ~10 % of patients at 5 years.

- **Bicuspid aortic valve (BAV):**

- BAV is the most common congenital heart disease (~1.3% of the population).
- It is more prevalent in men (3:1) and has a familial trend (36% have first-degree relative affected). Screening of the patient's children is appropriate.
- It is present in > 50% of patients with aortic coarctation and in ~10% of women with Turner syndrome.
- BAV is the most common cause of AS in patients < 70 years old (~two-thirds of AS). In patients older than 70 years, bicuspid AS is the cause of 40% of severe AS.
- Two of the three cusps are fused, most commonly the right and left cusps (80%), followed by the right and non-coronary cusps (20%). A residual raphe is often seen at the fusion site.
- The presence of two rather than three leaflets leads to a smaller surface in contact with the high-pressure stroke volume and marked leaflet bending, making the BAV more susceptible to shear stress. Progressive stress leads to calcific degeneration and AS later in life. The more asymmetrical the cusps are, the higher the stress is, and the faster AS develops.

- In early adult life (age of 20-50 years), 20% of BAV develop AI. AI may be related to: dilated aortic root, prolapse of the asymmetrically large cusp (can't support the extra weight of blood in diastole), myxoid degeneration with malcoaptation, endocarditis, or retraction of a fibrotic/calcified leaflet.
- Patients with BAV have a high risk of *ascending aortic dilatation or dissection*.
Aortic dilatation occurs in 50-60% of patients with BAV by the age of 30. This aortopathy is mainly secondary to cystic medial necrosis and is partly exaggerated by AS's post-stenotic dilatation or AI's volume and pressure load. As opposed to the aortic dilatation that may be seen with age and hypertension, this aortopathy frequently involves the aortic sinuses beside the tubular aorta.
Aortic dissection occurs in ~3-6% of BAV patients, ~60% of all dissections occur at a diameter < 5.5 cm.
- Patients with BAV should undergo, at least once, a screening with CT to assess the whole aorta.
A surveillance echo is recommended every year in patients with aortic size > 4 cm at the sinuses or higher, and every 2 years in bicuspid patients with aortic size < 4 cm.
- **Rheumatic Fever** (rare): in this case, AS almost always occurs with rheumatic involvement of the mitral valve and is often associated with severe AI.

Symptoms:

- **Dyspnea and reduced functional capacity:** related to the elevated LVEDP and the inability to raise cardiac output with exercise.
- **Syncope:** related to the fixed cardiac output that cannot increase with exertion **or** to the occurrence of arrhythmias. Vasodilatation occurs during exertion, but cardiac output cannot increase because of the fixed, severe outflow obstruction. Thus, the systemic pressure drops ($\text{Pressure} = \text{CO} \times \text{SVR}$).
- **Angina** occurs in two-thirds of the patients and is associated with CAD in 50% of these patients. In the other 50%, it results solely from increased O_2 demands (LVH) and reduced myocardial capillary perfusion (\uparrow LVEDP compresses the subendocardial microcirculation).

- **Bleeding tendency** (Heyde syndrome): GI bleeding from AV malformations due to the disruption of von Willebrand molecules as they cross the stenotic valve. This improves with AVR.

Natural History:

- Severe asymptomatic AS almost always becomes symptomatic within 5 years (~50% within 2 years) ⁽¹⁾, Severe asymptomatic AS is associated with low morbidity and mortality. Sudden death rate is < 1% per year.
- Severe symptomatic AS, on the other hand, is associated with a survival of 2-3 years only. Classically, the survival is ~3 years in patients with syncope, angina, or early dyspnea, and 1-2 years in patients with HF.
Sudden death is a frequent cause of death in symptomatic patients, thus justifying prompt surgery.
- AS progresses faster in patients with heavy calcifications or advanced renal failure. Some of the latter patients may progress from mild/moderate AS to severe AS within 3-4 years.

Evaluation:

▪ **Echocardiography:**

- Aortic valve velocity, which translates into transaortic pressure gradient ($4 \times \text{velocity}^2$), is the most important diagnostic feature of severe AS. However, Doppler may underestimate the pressure gradient if the cursor is not perfectly aligned with the transaortic flow. Therefore, the aortic velocity must be assessed in multiple views: the apical five- and three-chamber views, suprasternal view and a special right parasternal view, wherein the transducer is aligned with the ascending aorta ⁽²⁾.
- Aortic valve area (AVA) is calculated using the continuity equation and is subject to the additional pitfalls of measuring the LVOT diameter and velocity.

(1) Fast progression, similar to MR.

(2) The transaortic gradient is difficult to assess by TEE because only one view is aligned with the aortic flow, the transgastric long-axis view, a view that is not always obtainable.

Echocardiographic AVA measurement is less accurate and reproducible than the transaortic gradient. A high velocity/gradient is diagnostic of severe AS in a patient with a calcified, poorly mobile valve, regardless of AVA calculation. Doppler may, however, underestimate AS. On Doppler, a gradient > 40 mmHg is used as a more specific cutoff for defining severe AS, keeping in mind that a gradient of 30-40mmHg may be consistent with a normal-output severe AS, and a gradient of 15-30 mmHg may be consistent with a low-output severe AS.

| Table 11-10: Echocardiographic parameters of aortic stenosis: | | | |
|---|---------------------|------------------|---|
| | Mean transaortic PG | Peak AV velocity | Aortic Valve Area |
| Mild AS | < 20 mmHg | 2-2.9 m/s | > 1.5 cm ² |
| Moderate AS | 20-40 mmHg | 3-3.9 m/s | 1-1.5 cm ² |
| Severe AS | ≥ 40 mmHg | ≥ 4 m/s | ≤ 1 cm ² or indexed area 0.6 cm ² /m ² |

Other features suggestive of severe AS:

○ Dimensionless index:

While AV velocity ↑ (obstruction), LVOT velocity ↓ (reduced stroke volume). Typically, in severe AS:

- Peak LVOT velocity is < 1 m/s.
- LVOT velocity/aortic valve velocity is ≤ 0.25.

This is called the dimensionless index (DI). As opposed to AVA calculation, the DI is not subject to the bias of LVOT diameter measurement.

Pitfalls:

- LVOT velocity may be higher than 1 m/s when: **(i)** AS is associated with moderate AI or high-output states (anemia, fever). **(ii)** severe AS develop significant septal hypertrophy with septal bulge and LVOT obstruction (10% of patients). .
- Low-output states may lead to a low-gradient severe AS; the gradient is low, but LVOT velocity is < 1 m/s and DI is low, providing a hint to severe AS. DI does not allow, however, the distinction between severe AS and pseudo-severe AS.
- Like any velocity assessment, it is angle-dependent.

- **M-mode of the aortic valve shows flattening of the aortic box:** The aortic valve does not clearly open in the parasternal views. However, a BAV may appear to open moderately well on a parasternal view despite being severely stenotic. Since it only opens eccentrically between the non-coronary cusp and the fused cusp, the bicuspid valve is three-dimensionally more stenotic than it may appear on a two-dimensional view.

A bicuspid valve is characterized by **eccentric closure on M-mode** and, when not severely stenotic, systolic doming on the long-axis view.

- **AVA by planimetry.** Planimetry of the AVA is performed on the TEE short-axis view. The cut may be slightly above or below the true valvular orifice, which overestimates AVA.
- The lack of LVH is unusual but does not exclude AS. In fact, ~10% of AS patients do not develop concentric hypertrophy, and 4% do not even develop concentric remodeling. Those patients may have a higher mortality risk after AVR.

N.B:

☞ Transaortic pressure gradient is reduced in case of inappropriate tachycardia or short R-R interval (AF), and is increased after a PVC or a long R-R interval. The opposite occurs in MS.

Tachycardia may, however, be associated with an increase in transaortic gradient if inotropism and cardiac output are increased, as an increase in cardiac output strikingly increases the gradient.

☞ **In cases of AF:** Try to control the rate before assessment of AS and average the mean gradient from 5-10 beats. For echocardiographic AVA calculation, use VTI_{LVOT} and $VTI_{aortic\ valve}$ obtained after the same R-R cycle lengths.

Additional diagnostic and prognostic parameters:

- **Natriuretic peptides** predict symptom-free survival and outcome in normal and low-flow severe aortic stenosis. They can be used to arbitrate the source of symptoms in patients with multiple potential causes and identify those with high-risk asymptomatic aortic stenosis who may benefit from early intervention.
- **Exercise testing** may unmask symptoms and is recommended for risk stratification of asymptomatic patients with severe aortic stenosis. Exercise echocardiography provides additional prognostic information by assessing the increase in mean pressure gradient and change in LV function.

- **Cardiac CT** provides information concerning the anatomy of the aortic root and ascending aorta, and the extent and distribution of valve and vascular calcification, and feasibility of vascular access.
- **Cardiac MRI:** Myocardial fibrosis is a major driver of LV decompensation in aortic stenosis (regardless of the presence or absence of CAD), which can be detected and quantified using CMR. When cardiac amyloidosis is clinically suspected, based on symptoms (neuropathy and hematologic data), diphosphonate scintigraphy and/or CMR should be considered.
- **Catheterization:**

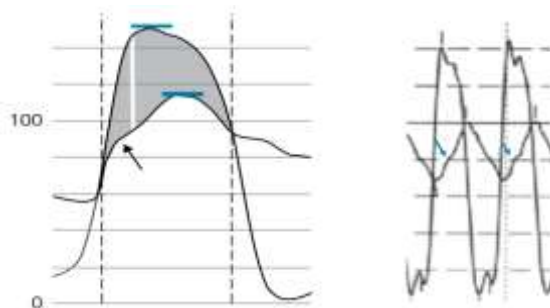


Figure 11-10: Aortic stenosis. Peak-to-peak gradient is the difference between the two peaks (blue bars), peak instantaneous gradient is the largest difference between the two curves (white vertical line), and mean gradient is the integration of all gradients (gray area). LV pressure peaks early and the aortic pressure peaks late, which is the opposite of what is found in HOCM. Note the *anacrotic notch* beyond which the aortic upstroke is slowed (arrows). The aortic upstroke starts normally then is sharply impeded after the valve stops opening, creating this bend called an anacrotic notch. The aortic pressure has a *slow upstroke after the anacrotic notch and peaks late (pulsus tardus)*. Also, the pulse pressure is reduced because of reduced stroke volume (*pulsus parvus*). In elderly patients with reduced arterial compliance, the pulse pressure may not be reduced and the anacrotic notch may be absent. The mean gradient usually approximates the peak to-peak gradient and is about 65% of the peak instantaneous gradient. In severe AS with severely delayed aortic upstroke, the mean gradient area may end up being larger than the peak-to-peak gradient. Note that, in AS, the aortic pressure upstroke is less steep than the LV pressure upstroke; if the LV and aortic upstrokes are superimposed, suspect subaortic obstruction or error in zeroing creating a false gradient (e.g., the LV and aortic transducers are zeroed at two different levels). **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Categories of Aortic Stenosis:

Current international recommendations for the echocardiographic evaluation of patients with aortic stenosis depend upon measurement of mean pressure gradient (the most robust parameter), peak transvalvular velocity (V_{\max}), and valve area. **Four broad categories can be defined:**

1. High-gradient AS ($AVA < 1 \text{ cm}^2$, mean gradient $> 40 \text{ mmHg}$).

Severe aortic stenosis can be assumed irrespective of whether LVEF and flow are normal or reduced.

2. Low-flow, low-gradient AS with reduced LVEF ($AVA < 1 \text{ cm}^2$, mean gradient $< 40 \text{ mmHg}$, $EF < 50\%$, stroke volume index (SV_i) $\leq 35 \text{ mL/m}^2$). Low-dose dobutamine echocardiography is recommended to:

- Distinguish truly severe AS from pseudosevere AS (an increase to an AVA of $> 1.0 \text{ cm}^2$ with flow normalization).
- In addition, the presence of flow reserve (also termed contractile reserve; increase of stroke volume $> 20\%$) has prognostic implications because it is associated with better outcome.

3. Low-flow, low-gradient AS with preserved LVEF ($AVA < 1 \text{ cm}^2$, mean gradient $< 40 \text{ mmHg}$, $LVEF \geq 50\%$, $SV_i \leq 35 \text{ mL/m}^2$).

The diagnosis of severe aortic stenosis in this setting remains challenging and requires careful exclusion of measurement errors and other reasons for such echocardiographic findings.

This is typically encountered in the elderly and is associated with small ventricular size, marked LVH and frequently a history of hypertension.

The degree of valve calcification by MSCT is related to aortic stenosis severity and outcome. Its assessment has therefore gained increasing importance in this setting.

4. Normal-flow, low-gradient AS with preserved LVEF ($AVA < 1 \text{ cm}^2$, mean gradient $< 40 \text{ mmHg}$, $LVEF \geq 50\%$, $SV_i > 35 \text{ mL/m}^2$).

These patients will in general have only moderate aortic stenosis.

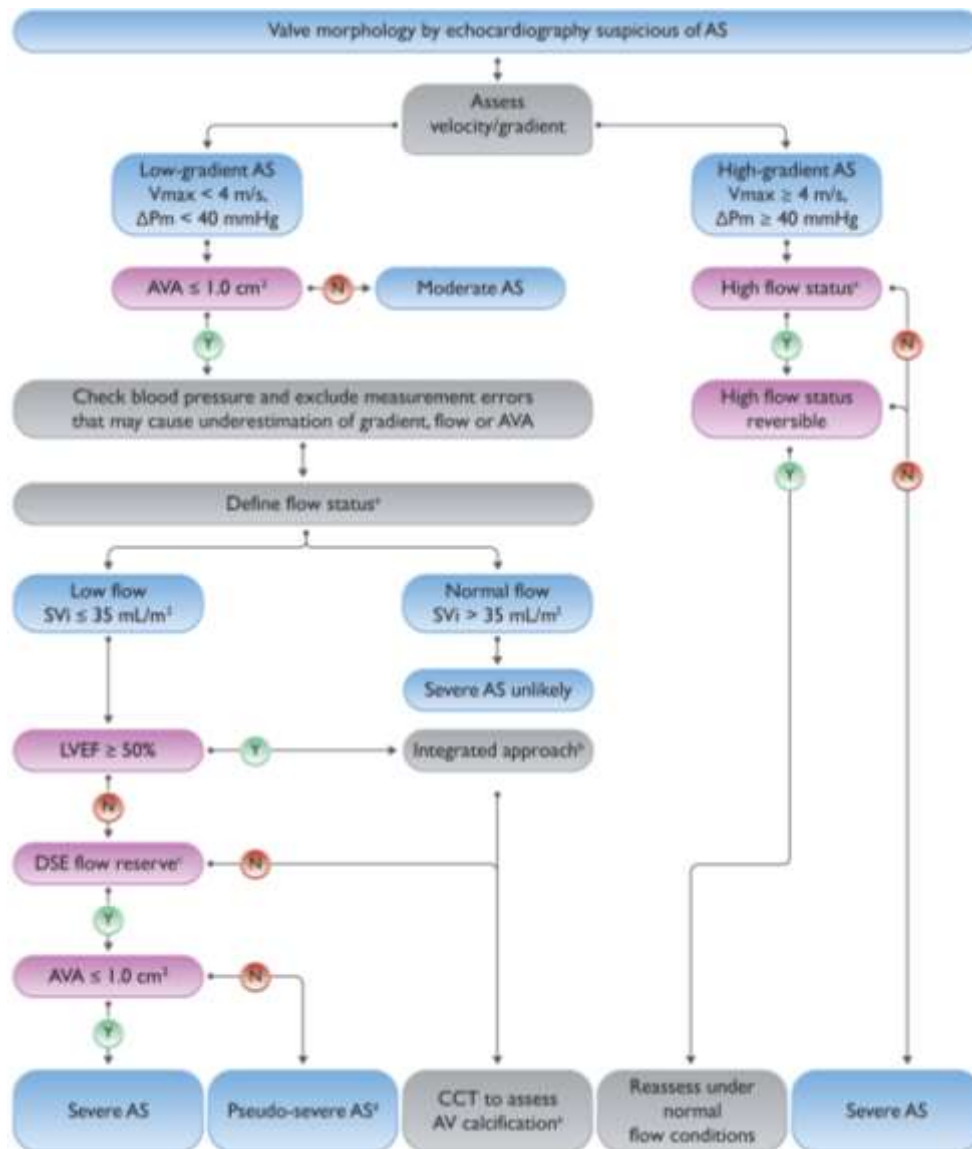


Figure 11-11: Integrated imaging assessment of aortic stenosis. A) High flow may be reversible in patients with anaemia, hyperthyroidism or AV fistulae, and may also be present in patients with HOCM. Upper limit of normal flow using pulsed Doppler echocardiography: cardiac index 4.1 L/min/m², SVi 54 mL/m² in men, 51 mL/m² in women). B) Consider also: typical symptoms (with no other explanation), LVH (in the absence of coexistent hypertension) or reduced LV longitudinal function (with no other cause). C) DSE flow reserve = > 20% increase in stroke volume in response to low-dose dobutamine. D) Pseudo-severe aortic stenosis= AVA > 1.0 cm² with increased flow. E) Thresholds for severe AS assessed by means of CT measurement of AV calcification (Agatston units): Highly likely= men > 3000, women > 1600; Likely= men > 2000, women > 1200; Unlikely= men < 1600, women < 800. **Source:** 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

▪ **Low-gradient AS with $AVA \leq 1 \text{ cm}^2$ and low EF < 50%:**

- In the case of a moderate-range mean gradient (30-40 mmHg) and $AVA \leq 1 \text{ cm}^2$, the patient likely has a **truly severe AS**.
- In case of mean gradient < 30 mmHg, $AVA \leq 1 \text{ cm}^2$, and EF < 50% (esp. < 40%), the patient may have:
 - **Truly severe AS** with a low gradient resulting from the low cardiac output, **or**
 - **Pseudo-severe AS** with a valve that is mildly or moderately stenotic, the excursion of which is further limited by the reduced cardiac output, leading to underestimation of the true AVA.
- A dobutamine study is indicated to increase the cardiac output and assess AS, and may be performed during *an echo or an invasive study*. Dobutamine is started as an infusion of 5 mcg/kg/min. The increase in cardiac output, AVA, and gradient are assessed then dobutamine up-titrated every 5-8 minutes if the diagnostic features are not met, the maximum dose being 20 mcg/kg/min. There are three possible responses:
 1. Stroke volume increases by $\geq 20\%$, gradient increases to > 30 mmHg, AVA remains unchanged or increases but remains $\leq 1.2 \text{ cm}^2$ (or increases < 0.2 cm^2): **truly severe AS with good contractile reserve**.
 2. Stroke volume increases by $\geq 20\%$, gradient remains $\leq 30 \text{ mmHg}$, and AVA increases to > 1.2 cm^2 : **pseudo-severe AS**.
 3. Stroke volume does not significantly increase (< 20%), gradient and AVA do not significantly change: **poor contractile or flow reserve**. This subgroup has the worst prognosis but may still benefit from AVR ⁽¹⁾.
- **Low-gradient AS with $AVA \leq 1 \text{ cm}^2$ but Normal EF (Paradoxical low-flow/Low-gradient Severe AS):**

A gradient is paradoxically low when it is < 40 mmHg or peak velocity is < 4 m/s despite $AVA \leq 1 \text{ cm}^2$.

 - A normal EF does not signify a normal cardiac output. Thus, even if EF is normal, patients with severe AS may have a reduced cardiac output that leads to a reduced gradient. This situation is seen in 10-20% of severe AS cases and usually reflects:
 - Severe preload reduction (e.g., hypovolemia)

(1) Before considering that the patient has a poor contractile reserve, Exclude hypovolemia and severely increased afterload from hypertension and high SVR. In this case, a careful nitroprusside infusion with titration may allow an increase in cardiac output, prove a good flow reserve, and allow evaluation of the severity of AS. Nitroprusside may precipitously drop the systemic pressure in patients with truly severe AS who cannot increase their cardiac output to match the dilated circulation, and should be used with great caution.

- Associated mitral valve disease that reduces the flow across the aortic valve.
- Severe hypertention. Hypertensive patients may have severe AS with a paradoxically low flow and low gradient due to: **(A)** increased total afterload, **(B)** concentric LVH with reduced LV cavity size.
- Thus, in these cases, AS is likely a truly severe AS with a low gradient due to a low stroke volume (= low-flow, low-gradient AS), and it is likely that the patient will benefit from aortic valve replacement. *Dobutamine testing is unlikely to be useful in these patients, as the preload and afterload are problematic, not contractility.*
- In comparison to a high transaortic gradient, a paradoxical low-flow, low-gradient severe AS is associated with a worse prognosis and lower survival with medical therapy compared to AVR. Survival is markedly improved with AVR.
- **When the diagnosis of paradoxical low flow/low gradient severe AS is suggested by echocardiography, the following is performed:**
 - **1st step:** Ensure appropriate measurements, particularly LVOT diameter (which should generally be > 2 cm). Also ensure acquisition of the highest AV velocity, aligned with the flow.
 - **2nd step:** Ensure that the indexed AVA is reduced < 0.6 cm²/m². AVA of 1 cm² may, in fact, correspond to moderate AS in a small patient.
 - **3rd step:** Measure the stroke volume index and valvuloarterial impedance.
 A low gradient associated with a normal stroke volume index > 35 ml/m² and a normal valvuloarterial impedance suggests that AS is not severe (normal-flow, low-gradient AS → AVA miscalculation, pressure recovery, or non-severe indexed AVA).
 A high LVOT velocity > 1 m/s rules out low cardiac output and thus rules out low-gradient AS. Similarly, a dimensionless index > 0.25 almost excludes low-gradient AS.
 - **4th step:** Low-gradient AS with normal EF frequently requires invasive measurements to confirm accurate gradient and valve area calculation, especially after control of HTN.

Table 11-11: Criteria making Severe AS more likely in patients with AVA < 1 cm² and mean PG < 40 mmHg in the presence of preserved EF:

Clinical Criteria

- *Typical symptoms without explanation.*

| | |
|----------------------------------|---|
| | <ul style="list-style-type: none"> ○ <i>Elderly patient (> 70 years).</i> |
| Qualitative Imaging Data | <ul style="list-style-type: none"> ○ <i>LVH (additional history of Hypertension to be considered).</i> ○ <i>Reduced LV longitudinal function without other explanation.</i> |
| Quantitative Imaging Data | <ul style="list-style-type: none"> ○ <i>Mean gradient 30-40 mmHg ⁽¹⁾</i> ○ <i>AVA $\leq 0.8 \text{ cm}^2$</i> ○ <i>Low flow (SVi < 35 ml/m²) confirmed by techniques other than standard doppler technique (LVOT measurement by 3D TEE or MSCT, CMR, invasive data)</i> ○ <i>Calcium Score by MSCT:</i> <ul style="list-style-type: none"> - <i>Severe AS very likely: Men ≥ 3000, Women ≥ 1600</i> - <i>Severe AS likely: Men ≥ 2000, Women ≥ 1200</i> - <i>Severe AS unlikely: Men <1600, Women < 800</i> |

Notes:

➤ Pressure recovery phenomenon:

In patients with AS, pressure (potential energy) is generated by the LV. A significant portion of this energy is lost across the narrow aortic valve orifice and becomes kinetic energy.

Downstream from the valve, the flow becomes laminar again and there may be a reincrease in pressure and in potential energy, particularly in female patients with a narrow aorta (diameter at the sinotubular junction < 3 cm). This reincrease in pressure downstream of the valve is called “**pressure recovery**”.

The true gradient is the gradient between LV pressure and the pressure downstream of the valve. This gradient represents the true loss of energy the ventricle is subject to.

(1) Hemodynamics measured when the patient is normotensive.

In this case, the transaortic gradient obtained by echo is the pressure gradient between the LV and the vena contracta and overestimates the physiologic AS; in addition, AVA calculated by the echocardiographic continuity equation overestimates the severity of AS.

In practice, *Echocardiography much more often underestimates than overestimates AS gradient, and thus, gradient > 40 mmHg is usually severe AS even if AVA is calculated as > 1 cm².*

➤ **AS should be differentiated from Subvalvular and Supravalvular AS in children or young adults:**

While the majority of congenital aortic obstructions are due to bicuspid AS, 14% are due to fixed subvalvular AS, and a minority are due to supravalvular AS. The two conditions mainly present in children or young adults.

● **Diagnosis of subvalvular or supravalvular AS:**

- In both conditions, **Doppler** shows high velocity across the transaortic plane with a structurally normal aortic valve. The actual site of narrowing/membrane may be seen. On color Doppler, the turbulence is seen below or above the aortic valve. TEE may be required in young patients to define this anatomy.

- **On examination,** A2 is loud rather than attenuated (≠ AS) and a systolic click is not heard (≠ bicuspid AS).

In subvalvular AS, the murmur does not consistently radiate to the carotids.

In supravalvular AS, the narrow jet goes preferentially towards the right side of the aorta as it abuts the aortic wall, and thus the pulses are stronger in the right vs. left arm, and the murmur only radiates to the right carotid with suprasternal thrill.

- **Invasively,** pressure pullback with an end-hole catheter confirms the site of obstruction; in contrast to HOCM, the gradient is not dynamic and does not have a dagger shape.

● **Subvalvular AS:**

- Fixed subvalvular AS is present at birth and is most often caused by a *discrete fibrous membrane* that encircles the outflow tract beneath the aortic valve. The aortic valvular leaflets are commonly thickened and regurgitant as a result of the turbulent blood flow jet caused by the subvalvular stenosis.
- Less commonly, a thick fibromuscular ridge or prolonged LVOT thickening (tunnel obstruction) is seen.
- It is commonly associated with VSD.

- Surgical therapy is indicated in fixed subvalvular stenosis to prevent the progressive AI that is seen in > 80% of untreated patients, regardless of symptoms (as long as mean gradient > 30 mmHg).
- **Supravalvular AS:**
 - Supravalvular stenosis results from aortic narrowing at the superior margin of the aortic sinuses. Stenosis may be a *focal hourglass type of narrowing* (most common form), a discrete supravalvular membrane, or diffuse hypoplasia of the ascending aorta (the least common form).
 - Like the aortic sinuses, the coronary arteries are subject to large systolic and pulse pressures, as the stroke volume overfills the small aortic chamber prior to the obstruction. Frequently, the coronary arteries are diffusely dilated and develop ostial stenoses.
 - Aortic valve thickening and regurgitation may develop.
 - This condition is frequently associated with peripheral pulmonary artery stenosis.
 - Supravalvular AS is often non-syndromic but may be associated with Williams syndrome (hypercalcemia, elfin facies, mild mental retardation) and may be genetically transmitted.
 - Surgical therapy is indicated if: Symptomatic, LVH, or Asymptomatic with mean gradient > 50 mmHg.

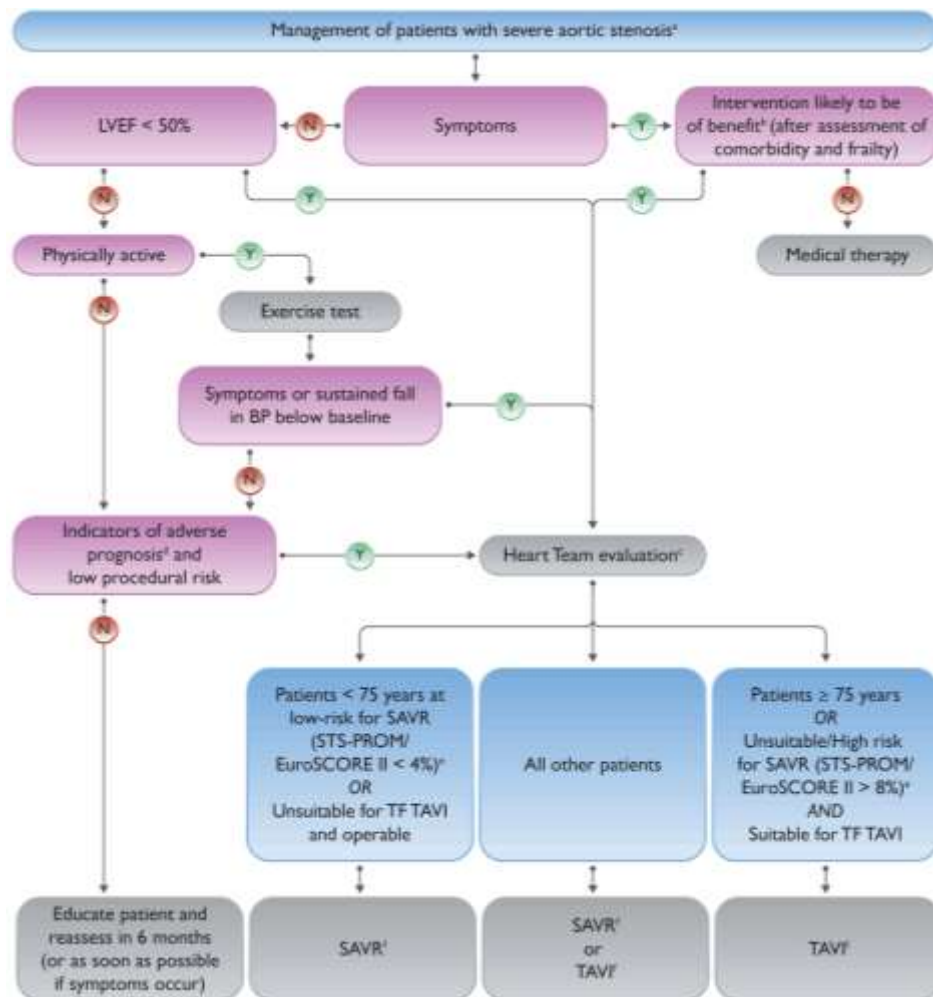


Figure 11-12: Management of patients with severe aortic stenosis. B) Prohibitive risk is defined as PARTNER TAVI or FRANCE 2 TAVI Risk score ≥ 8 (30-day mortality risk $> 25\%$), Katz Index ≥ 4 indices and ≥ 3 organ systems compromise not to be improved post-TAVI. **C)** Heart Team assessment based upon careful evaluation of clinical, anatomical, and procedural factors. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice. **D)** Adverse features according to clinical, imaging and/or biomarker assessment. **E)** STS-PROM: <http://riskcalc.sts.org/stswebriskcalc/#/calculate>, EuroSCORE II: <http://www.euroscore.org/calc.html>. **F)** If suitable for procedure according to clinical, anatomical, and procedural factors. **Source:** 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

▪ **Indication for intervention:**

| Table 11-12: ESC Recommendations on indications for intervention (SAVR or TAVI) in symptomatic (A) and asymptomatic (B) aortic stenosis and recommended mode of intervention (C): | | |
|---|-------|-------|
| Recommendations | Class | Level |
| A) Symptomatic aortic stenosis: | | |
| Intervention is recommended in symptomatic patients with: | | |
| ○ Severe, high-gradient AS [mean gradient ≥ 40 mmHg, peak velocity ≥ 4.0 m/s, and AVA ≤ 1.0 cm ² (or ≤ 0.6 cm ² /m ²)]. | I | B |
| ○ Severe low-flow (SVI ≤ 35 mL/m ²), low-gradient (< 40 mmHg) AS with reduced EF ($< 50\%$), and evidence of flow (contractile) reserve. | | |
| Intervention should be considered in symptomatic patients with low-flow, low-gradient (< 40 mmHg) AS with: | IIa | C |
| ○ Normal LVEF after careful confirmation that the aortic stenosis is severe ⁽¹⁾ | | |
| ○ reduced LVEF without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe aortic stenosis. | | |
| Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival > 1 year. | III | C |
| B) Asymptomatic patients with severe aortic stenosis | | |
| Intervention is recommended in asymptomatic patients with severe AS and: | | |
| - Systolic LV dysfunction (LVEF $< 50\%$) without another cause. | I | B |
| - demonstrable symptoms on exercise testing. | I | C |
| Intervention should be considered in asymptomatic patients with severe AS and: | | |

(1) Explanations other than severe AS for a small AVA but low gradient despite preserved LVEF are frequent and must be excluded.

| | | |
|--|-----|---|
| - Systolic LV dysfunction (LVEF < 55%) without another cause. | IIa | B |
| - Sustained fall in BP (> 20 mmHg) during exercise testing. | IIa | C |
| Intervention should be considered in asymptomatic patients with LVEF > 55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: | IIa | B |
| - Very severe aortic stenosis (mean gradient \geq 60 mmHg or V_{max} > 5 m/s). | | |
| - Severe valve calcification (ideally assessed by CCT) and V_{max} progression \geq 0.3 m/s/year. | | |
| - Markedly elevated BNP levels (> 3 age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation. | | |
| C) Mode of intervention: | | |
| Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach. | I | C |
| The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice. | I | C |
| SAVR is recommended in younger patients who are low risk for surgery (< 75 years and STS PROM/EuroSCORE II < 4%) or in patients who are operable and unsuitable for transfemoral TAVI. | I | B |
| TAVI is recommended in older patients (\geq 75 years), or in those who are high risk (STS PROM/EuroSCORE II > 8%) or unsuitable for surgery. | I | A |
| SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics. | I | B |

| | | |
|---|------------|----------|
| <i>Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.</i> | IIb | C |
| <i>Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients and (if feasible) in those with severe aortic stenosis who require urgent high risk NCS</i> | IIb | C |
| D) Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery: | | |
| <i>SAVR is recommended in patients with severe AS undergoing CABG or surgical intervention on the ascending aorta or another valve.</i> | I | C |
| <i>SAVR should be considered in patients with moderate AS ⁽¹⁾ undergoing CABG or surgical intervention on the ascending aorta or another valve after Heart Team discussion.</i> | IIa | C |

Surgical Vs Transcatheter AVR:

The high prevalence of comorbidity in the elderly makes assessment of the risk/benefit ratios of interventions more difficult, therefore the role of the Heart Team is essential in this specific population.

- Initially, futility should be avoided. Therapeutic futility has been defined as a lack of medical efficacy, particularly when the physician judges that the therapy is unlikely to produce its intended clinical results, or lack of meaningful survival according to the personal values of the patient. Prohibitive risk is defined as PARTNER TAVI or FRANCE 2 TAVI Risk score ≥ 8 (30-day mortality risk $> 25\%$), Katz Index ≥ 4 indices and ≥ 3 organ systems compromise not to be improved post-TAVI.
- Risk stratification:** Risk stratification is required for weighing the risk of intervention against the expected natural history of VHD and for choosing the type of intervention.

(1) Moderate AS is defined as a valve area of 1.0-1.5 cm² (or mean aortic gradient of 25-40 mmHg) in normal flow conditions-clinical assessment is essential to determine whether SAVR is appropriate for an individual patient.

1. **Risk scores:** The STS-PROM score (<http://riskcalc.sts.org/stswebriskcalc/calculate>) and the EuroSCORE II (<http://www.euroscore.org/calc.html>) accurately discriminate high- and low-risk surgical patients and show good calibration to predict postoperative outcome after valvular surgery.
2. **Frailty**, defined as a decrease of physiologic reserve and ability to maintain homeostasis leading to an increased vulnerability to stresses and conferring an increased risk of morbidity and mortality after both surgery and TAVI. The assessment of frailty should not rely on a subjective approach, such as the 'eyeball test'. Several tools are available for assessing frailty.
3. **Malnutrition and cognitive dysfunction.**
4. **Other major organ failures:** e.g., severe lung disease in patients undergoing SAVR via full sternotomy may contribute to pulmonary complications.
5. **Anatomical aspects** affecting procedural performance such as porcelain aorta or severe MAC.
 - **Surgical aortic valve replacement (SAVR):**
 - The mortality risk of AVR is ~3%, and may be as low as 1-2% in low-risk young patients and as high as 10% in patients with low EF, especially low EF with low-gradient AS.
 - Concomitant CAD, particularly multivessel CAD requiring CABG, increases the perioperative mortality, especially in octogenarians (up to 18%). In fact, leaving CAD untreated increases the perioperative risk of ischemia and MI, so CABG is rather useful for these patients.
 - As opposed to valvular regurgitation, LV dysfunction very rarely develops in AS before symptoms (unless due to other causes, e.g., CAD). LV dysfunction improves more readily in patients with AS than in those with AI or MR, as it is usually due to *afterload mismatch* rather than contractile/fibrotic dysfunction. LV mass decreases over the course of one to several years postoperatively.
 - **Transcatheter aortic valve replacement (TAVR):**
 - **Access:** TAVR may be performed through a transfemoral, transaxillary, or transcaval approach. It may also be performed surgically through a transapical or direct ascending aortic approach.

- **Types of valves:** The valve is a balloon expandable valve (e.g., Edwards Sapien valves) or a self-expanding valve (e.g., Medtronic Evolut R, Boston Acurate Neo) or a mechanically-expandable valves (e.g., Lotus).
- Anatomical limitations:
 - (i) TAVR is *not* typically used in patients with a *clearly bicuspid* valve, where the aortic opening is elliptical rather than circular, which prevents symmetrical apposition of the cylindrical prosthesis and allows paravalvular leaks. This is only a relative contraindication, particularly because in many critical AS cases, the tight residual orifice does not allow distinction between tricuspid and bicuspid valves.
 - (ii) The use of TAVR in severe AI is limited by:
 - Coexistent aortic root disease and large annular size increase the risk of dehiscence and persistent AI;
 - Frequent lack of significant valvular calcifications, which serve as a fluoroscopic landmark for valve positioning and as an anchor at the lower part of the stent frame;
 - Difficulty in positioning in a patient with regurgitant jet.
- **Complications:** TAVR is associated with a 5% rate of postoperative stroke. Moderate or severe paravalvular regurgitation is common (10%) and is associated with early and long-term increase in mortality, particularly with the balloon-expandable valves. Conversely, the Corevalve trial revealed that paravalvular AI improves at 1 year to less than mild in 75% of patients with moderate/severe AI, thanks to the sustained expansion of the self-expanding frame.
- **TAVI diagnostic workup:** Prior to TAVI, Cardiac CT is the preferred imaging tool to assess:
 - Aortic valve anatomy, Annular size and shape.
 - Extent and distribution of valve and vascular calcification.
 - Risk of coronary ostial obstruction and Aortic root dimensions.
 - Feasibility of vascular access (femoral, subclavian, axillary, carotid, transcaval or transapical).

Table 11-13: Clinical, anatomical and procedural factors that influence the choice of treatment modality for an individual patient:

| | Favours TAVI | Favours SAVR |
|--|------------------|--------------|
| Clinical characteristics: | | |
| <i>Lower surgical risk</i> | - | + |
| <i>Higher surgical risk</i> | + | - |
| <i>Younger age</i> | - | + |
| <i>Older age</i> | + | - |
| <i>Previous cardiac surgery (particularly intact coronary artery bypass grafts at risk of injury during repeat sternotomy)</i> | + | - |
| <i>Severe frailty ⁽¹⁾</i> | + | - |
| <i>Active or suspected endocarditis</i> | - | + |
| Anatomical and procedural factors: | | |
| <i>TAVI feasible via transfemoral approach</i> | + | - |
| <i>Transfemoral access challenging or impossible and SAVR feasible.</i> | - | + |
| <i>Transfemoral access challenging or impossible and SAVR inadvisable.</i> | + ⁽²⁾ | - |
| <i>Sequelae of chest radiation</i> | + | - |
| <i>Porcelain aorta</i> | + | - |
| <i>High likelihood of severe patient prosthesis mismatch (AVA < 0.65 cm²/m² BSA)</i> | + | - |
| <i>Severe chest deformation or scoliosis</i> | + | - |
| <i>Aortic annular dimensions unsuitable for available TAVI devices</i> | - | + |
| <i>Bicuspid aortic valve</i> | - | + |

(1) Severe frailty = > 2 factors according to Katz index

(2) Via non-transfemoral approach.

| | | |
|--|---|---|
| <i>Valve morphology unfavourable for TAVI (e.g. high risk of coronary obstruction due to low coronary ostia or heavy leaflet/LVOT calcification)</i> | - | + |
| <i>Thrombus in aorta or LV</i> | - | + |
| Concomitant cardiac conditions requiring intervention: | | |
| <i>Significant multi-vessel CAD requiring surgical revascularization</i> | - | + |
| <i>Severe primary mitral valve disease</i> | - | + |
| <i>Severe tricuspid valve disease</i> | - | + |
| <i>Significant dilatation/aneurysm of the aortic root and/or ascending aorta</i> | - | + |
| <i>Septal hypertrophy requiring myectomy</i> | - | + |

N.B: Ross procedure:

The Ross procedure consists of pulmonary artery + pulmonic valve autograft placement in the aortic position, while a homograft valve is placed in the pulmonary position. This procedure is mainly used in young patients. It has the advantage of not requiring anticoagulation. Moreover, the autograft grows when used in children. However, this procedure should be avoided in cases of AI with dilated ascending aorta, as the dilated aorta will put tension on the grafted pulmonary artery, with a risk of neo-aortic root dilatation and late AI. Also, a long-term risk of pulmonic stenosis and/or regurgitation of the homograft and AI of the neo-aorta is seen.

▪ **Medical therapy:**

- No medical therapy for aortic stenosis can improve outcome compared with the natural history.
- Patients with symptoms of HF who are unsuitable candidates for surgery or TAVI or who are currently awaiting surgical or catheter intervention should be medically treated according to the HF guidelines.

- HTN is common in AS (~1/3 of patients), worsens LV afterload, and leads to double loading of the LV with a low-flow/low-gradient state. Antihypertensives (e.g., vasodilators) may be harmful in AS ⁽¹⁾ , but should be carefully used if HTN coexists to reduce the total afterload and increases cardiac output.

Follow-up:

Rate of progression of aortic stenosis varies widely. Asymptomatic patients, their family and medical carers need careful education, with emphasis on the importance of regular follow-up.

- Those with severe AS should be followed up every **6 months** (at least) to allow earliest symptom detection (using exercise testing if symptoms are doubtful) and any change in echocardiographic parameters (particularly LVEF). Measurement of natriuretic peptides may be considered.
- Patients with moderate degenerative AS is worse than previously considered (particularly if there is significant valve calcification) and these patients should be reevaluated at least **annually**.
- Younger patients with mild AS and no significant calcification may be followed up every 2-3 years.

Special patient populations:

- **CAD associated with severe AS:** The impact of coronary revascularization in patients with silent CAD accompanying aortic stenosis is unclear and further studies are warranted in this context.
- Both simultaneous SAVR and CABG, and SAVR late after CABG, carry a higher procedural risk than isolated SAVR.
- Retrospective data indicate that patients with moderate AS, in whom CABG is indicated, benefit from concomitant SAVR. Patients aged < 70 years with mean gradient progression ≥ 5 mmHg/year benefit from SAVR at the time of CABG once baseline peak gradient exceeds 30 mmHg. Decisions for individual patients should take into account haemodynamic data, rate of

(1) Normally, when vasodilators are administered, the systemic pressure is maintained thanks to an increase in cardiac output ($\text{Pressure} = \text{CO} \times \text{Resistance}$). Severe AS may limit the increase in cardiac output, and thus severe hypotension may ensue.

progression, extent of leaflet calcification, life expectancy, and associated comorbidities, as well as the individual risk of concomitant SAVR or deferred TAVI.

- PCI and TAVI may be undertaken as combined or staged procedures according to the clinical situation, pattern of CAD, and extent of myocardium at risk. Patients with severe symptomatic AS and diffuse CAD unsuitable for revascularization should receive optimal medical therapy and undergo SAVR or TAVI according to individual characteristics.

- **MR associated with severe AS:**

MR frequently coexists with severe AS and is often functional, secondary to LV and LA remodeling and the increased LV systolic pressure (> 15% of AS patients have moderate or severe MR). Severity of MR accompanying severe AS may be overestimated as a result of elevated LV pressures and careful quantification is required.

- In patients with severe PMR, mitral valve surgery is required at the time of SAVR.
- In patients with severe SMR, MR often improves in 50-90% of patients after AVR, but mitral valve surgery may be considered in the presence of significant annular dilatation and marked LV enlargement.
- In high-risk or inoperable patients with severe AS and severe MR, combined (or more often sequential) TAVI and TEER may be feasible.
- In patients with severe PMR, TEER should be considered early if the patient remains symptomatic and MR is still severe after TAVI.
- In patients with severe SMR, TAVI should be followed by careful clinical and echocardiographic reassessment to determine whether further mitral intervention is required.

Aortic Insufficiency

Aetiology:

- **Chronic AI:** Aortic regurgitation can be caused by primary disease of the aortic valve cusps and/or abnormalities of the aortic root and ascending aortic geometry.
- **Dilatation of the ascending aorta with secondary AI:** this is the most common cause of severe AI.
While potentially causing AI, aortic dilatation is reciprocally worsened by the high stroke volume of AI; it is also worsened by the high post-stenotic jet of AS (post-stenotic dilatation).
Causes of ascending aortic disorders:
 - Degenerative aortic dilatation, related to age and hypertension, is the most common cause.
 - Cystic medial necrosis, which occurs in younger patients: **(1)** Marfan or Marfan fruste, **(2)** Bicuspid aortic valve, **(3)** Spondyloarthropathies.
- **Aortic valve disorders:**
 - Bicuspid aortic valve is the most common valvular cause of severe AI. AI results from prolapse of a leaflet or incomplete closure of a thickened redundant valve.
 - Old, healed endocarditis.
 - Idiopathic degeneration of the aortic valve with increased and disorganized collagen and elastic fibers.
 - Rheumatic fever with fibrosis and retraction of the leaflets. Fibrosis and fusion of the commissures also leads to AS. The aortic valve is immobile and does not open or close (combined AS/AI).
 - Prolapse of an aortic valve leaflet in the context of bicuspid aortic valve, endocarditis, trauma, or myxomatous degeneration.
 - Degeneration of a bioprosthesis.
- **Acute AI:**
 - **Endocarditis:** the vegetation may perforate the leaflet(s) or prevent valvular coaptation.

- **Aortic dissection** leads to AI through three potential mechanisms:
 - dilatation of the sinotubular junction.
 - dissection extends into the leaflet attachment at the sinotubular junction, resulting in leaflet prolapse and eccentric AI.
 - dissection flap prolapses through the aortic orifice and prevents leaflet coaptation.
- **Closed chest trauma** may lacerate the aortic leaflet or its sinotubular insertion, causing it to prolapse. Being anterior, the aortic valve is the valve most commonly involved in chest trauma.

Pathophysiology and hemodynamics:

- **Chronic compensated AI:**

- In chronic compensated AI, LV volume increases, the total stroke volume increases, leading to a high pulse pressure (e.g., 160/60 mmHg), and the forward stroke volume is maintained. The LV is large and compliant in a way that it accommodates the regurgitant volume without an increase in LVEDP. The aortic and LV pressures do not approximate at the end of diastole; on Doppler, this corresponds to a gradual rather than steep drop of the regurgitant flow velocity with a pressure half-time that is > 250 ms, even if AI is severe.
- While a wide pulse pressure ($> \frac{1}{2}$ SBP or > 60-80 mmHg) is a very sensitive finding in chronic severe AI, it is not a specific finding and may be seen in a poorly compliant aorta and in high-output states with low afterload (patent ductus arteriosus, hyperthyroidism, anemia, fever, and arteriovenous fistula).
- The peripheral femoral pressure may get excessively amplified and may exceed the central systolic pressure by 50 mmHg or more. This is an exaggeration of a normal effect and is due to the hyperdynamic state and the excess of reflected waves in the periphery. These reflected waves may explain a second systolic pressure peak in the peripheral arteries and aorta (*Pulsus bisferiens*).

- **Chronic decompensated AI:**

In chronic decompensated AI, the LV function starts to decline, and EF decreases such that the forward stroke volume declines and the LV volume further increases. This leads to increased LVEDP despite good LV compliance. Similarly to acute AI, LV and

aortic pressures approximate in end-diastole. On Doppler, this corresponds to a steep drop of regurgitant flow velocity throughout diastole with a short pressure half-time < 250 ms. Total stroke volume remains elevated, and thus the pulse pressure remains elevated. At an advanced stage, when EF is severely reduced, total stroke volume and pulse pressure may decline.

▪ **Acute AI:**

- In acute AI, LV is non-compliant and LV volume is normal. Thus, the regurgitant volume leads to a severe increase in LVEDP. LV diastolic pressure exceeds LA pressure in mid- or late-diastole, leading to a reverse LV-LA gradient and forcing the mitral valve to close prematurely (functional MS), a finding typical of decompensated AI.
- Since LV is not dilated, the stroke volume is reduced in acute AI. Therefore, in addition to the low DBP, SBP is usually low (e.g., BP 90/40 mmHg).
- As opposed to chronic AI, pulse pressure is only mildly widened, but this already suggests acute AI in a patient with acute heart failure, wherein the arterial pulse pressure is typically narrow.
- Tachycardia is an important compensatory response in acute AI as it increases the cardiac output and reduces the regurgitant time, and thus should be respected.

N.B:

- ☞ As opposed to other valvular disorders, chronic AI is well tolerated during exercise. In fact, tachycardia reduces diastole and the time available for regurgitation, and the vasodilatation associated with exercise reduces the regurgitant volume, which allows an increase in cardiac output during exercise.
- ☞ Severe AI, as opposed to MR, is well tolerated for years before symptoms develop. In AI, volume overload must surpass the compliance of the LV then the compliance of the LA to provoke pulmonary edema, whereas in MR only surpassing the compliance of the LA is necessary. Symptoms develop very gradually and the patient adapts to them over the years, sometimes not realizing the change in functional status.
- ☞ Both preload and afterload are increased in severe AI. The LV dilatation increases wall stress, i.e., afterload, which is proportional to both the LV systolic pressure and the LV radius. Eccentric LV hypertrophy allows the LV to adapt to this load

increase. Initially, the EF reduction results from the progressive increase of LV size and afterload rather than an intrinsic LV contractile dysfunction (**afterload mismatch**). *This process is fully reversible with AVR and is different from the early decline of EF in MR, which already implies a significant contractile dysfunction that may be irreversible.*

Natural history and symptoms:

- Asymptomatic severe AI with normal LV function has a slow progression: < 0.2% sudden cardiac death per year, 4.5% progression to symptoms and/or LV dysfunction per year.
Patients with LVEDS > 50 mm or LVEDD > 70 mm have the highest risk of progression to symptoms and/or LV dysfunction (10-20% per year). AI symptoms appear late in the disease process, usually after LV has severely enlarged. Class II *dyspnea* appears earlier than *angina* and *severe HF*.
- Subendocardial coronary flow being driven by the gradient between aortic diastolic pressure and LVEDP, angina is often functional and related to the severe drop in aortic diastolic pressure and the increase in LVEDP. Moreover, O₂ demands of the large LV are severely increased.
- Angina may be nocturnal rather than exertional, aggravated by bradycardia, wherein the aortic diastolic pressure decreases to very low levels. Diastolic reversal of coronary flow may be seen in severe cases.
- *Palpitations* may appear early on and are related to the ejection of a large LV volume, especially after a PVC; they are not, per se, an indication for surgery.

Diagnosis:

- **Transthoracic Echocardiography:** TTE is the key examination used to describe valve anatomy, quantify aortic regurgitation, evaluate its mechanisms, define the morphology of the aorta, and determine the feasibility of valvesparing aortic surgery or valve repair. Identification of the mechanism follows the same principle such as for mitral regurgitation: normal cusps but insufficient coaptation due to dilatation of the aortic root with central jet (type 1), cusp prolapse with eccentric jet (type 2), or retraction with poor cusp tissue quality and large central or eccentric jet (type 3).

| Table 11-14: Echocardiographic criteria for the definition of severe aortic valve regurgitation: | |
|--|---|
| Qualitative: | |
| Valve morphology | <i>Abnormal/flail/large coaptation defect</i> |
| Colour flow regurgitant jet area | <i>Large in central jets, variable in eccentric jets</i> |
| CW signal of regurgitant jet | <i>Dense</i> |
| Other | <i>Holodiastolic flow reversal in descending aorta (EDV > 20 cm/s)</i> |
| Semiquantitative: | |
| Vena contracta width (mm) | <i>> 6</i> |
| Pressure half-time (ms) | <i>< 200</i> |
| Quantitative: | |
| EROA (mm ²) | <i>≥ 30</i> |
| Regurgitant volume (mL/beat) | <i>≥ 60</i> |
| Enlargement of cardiac chambers | <i>LV dilatation</i> |

Measurement of the aortic root and ascending aorta in 2D is performed at four levels: annulus, sinuses of Valsalva, sinotubular junction, and tubular ascending aorta. Measurements are performed in the parasternal long-axis view from leading edge to leading edge at end diastole, except for the aortic annulus, which is measured in mid systole. As it will have surgical consequences, it is important to differentiate three phenotypes of the ascending aorta: aortic root aneurysms (sinuses of Valsalva > 45 mm), tubular ascending aneurysm (sinuses of Valsalva < 40-45 mm), and isolated aortic regurgitation (all aortic diameters < 40 mm). The calculation of indexed values to account for body size has been suggested, in particular in patients with small stature.

▪ **Transesophageal Echocardiography:**

- TOE is not significantly superior to TTE for the assessment of the severity of AI. TOE is superior for the anatomical assessment of the aortic valve and aortic annulus (bicuspid morphology, endocarditis), and for the assessment of the ascending aorta.
- TOE is used for definition of the *anatomy of the aortic valve cusps* and assessment of valve reparability should be provided by preoperative TOE if aortic valve repair or a valve-sparing surgery of the aortic root is considered.
- TOE is used for *Intraoperative evaluation* of the surgical result by TOE is mandatory in patients in whom the aortic valve is preserved or repaired in the procedure.

▪ **Cardiac CT and MRI:**

CMR should be used to quantify the regurgitant fraction when echocardiographic measurements are equivocal or discordant with clinical findings. In patients with aortic dilatation, CCT is recommended to assess the maximum diameter at four levels, as in echocardiography. CMR can be used for follow-up, but indication for surgery should preferably be based on CCT measurements. Maximum root diameter should be taken from sinus to-sinus diameter rather than sinus-to-commissure diameter, as it correlates more closely to long-axis leading edge to leading edge echo maximum diameters.

▪ **Aortic root angiography and hemodynamic measurements:** Hemodynamically, severe AI is characterized by four features:

- (1) Wide aortic pulse pressure, particularly seen in chronic AI.
 - (2) Loss of the aortic dicrotic notch, particularly seen in acute AI.
 - (3) LV end-diastolic pressure approximates aortic pressure.
 - (4) LV end-diastolic pressure exceeds mean PCWP.
- (the last two findings are seen with acute or chronic decompensated AI).

Table 11-15: Peripheral signs of Aortic Regurgitation:

Head and Neck:

| | |
|------------------------------|--|
| Alfred de Musset sign | Head nodding with heartbeat |
| Lighthouse sign | Blanching and flushing of the forehead. |
| Corrigan sign | Prominent carotid and supraclavicular pulsations |

| | |
|---------------------------|---|
| Landolfi sign | Change in pupil size with heartbeat. |
| Becker sign | Retinal artery pulsations |
| Muller sign | Uvula pulsations |
| Abdomen: | |
| Rosenbach sign | Liver pulsations |
| Gerhardt sign | Spleen pulsations |
| Upper Limb: | |
| Quincke sign | Digital capillary pulsations |
| Water-Hammer pulse | High volume abruptly collapsing pulse. |
| Mayne sign | Diastolic BP drop of > 15 mmHg with arm raised. |
| Lower Limb: | |
| Trauble sign | “Pistol shot”- systolic and diastolic booming sound over femoral artery |
| Deroziez sign | Intermittent to and fro femoral artery systolic and diastolic murmur generated by light compression with the bell of a stethoscope. |
| Hill sign | Lower limb systolic BP exceeding upper limb systolic BP > 20 mmHg. |
| Lincoln sign | Pulsatilla popliteal artery |
| Sherman sign | Dorsalis pedis pulse unexpectedly prominent in age > 75 years |

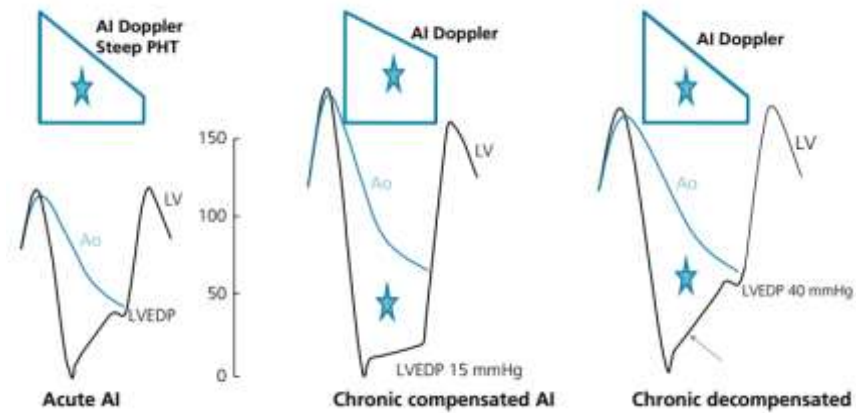


Figure 11-13: LV-aortic pressure tracings in acute AI and chronic AI. In acute and decompensated AI, the steep diastolic approximation of LV and aortic pressures (triangle, star) translate into a similarly steep AI Doppler. Conversely, in compensated AI, LV and aortic pressures do not approximate in end-diastole. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Management:

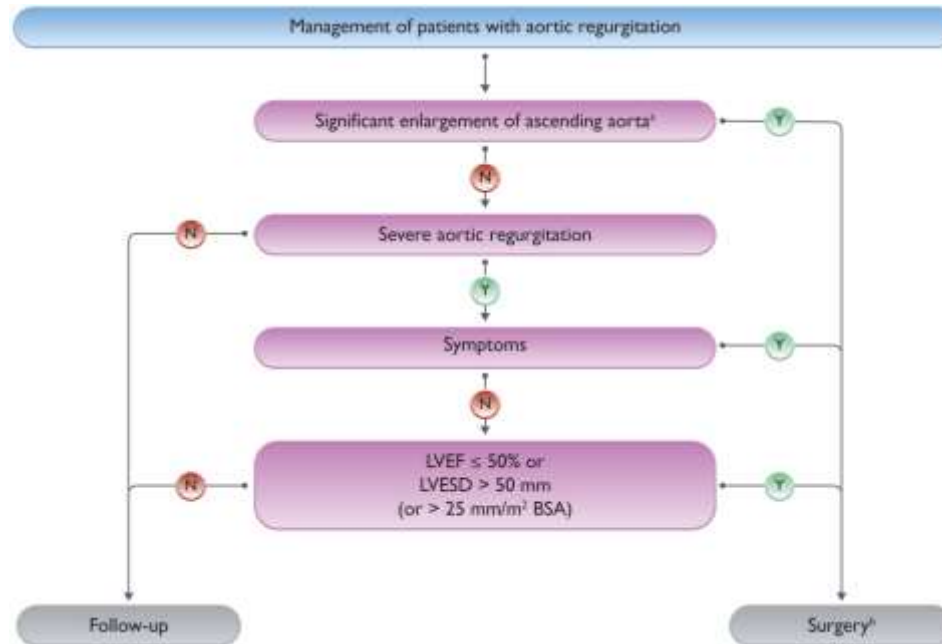


Figure 11-14: Management of patients with aortic regurgitation. A) See recommendations on indications for surgery in severe aortic regurgitation and aortic root disease for definition. B) Surgery should also be considered if significant changes in LV or aortic size occur during follow-up. **Source:** 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

▪ **Indication for intervention:**

Table 11-16: ESC Recommendations on indications for surgery in (A) severe aortic regurgitation and (B) aortic root or tubular ascending aortic aneurysm (irrespective of the severity of aortic regurgitation):

| Indications for surgery | Class | Level |
|---|-------|-------|
| A) Severe aortic regurgitation: | | |
| <p><i>Surgery is recommended in:</i></p> <ul style="list-style-type: none"> ○ <i>Symptomatic patients regardless of LV function.</i> ○ <i>Asymptomatic patients with LVESD > 50 mm or LVESD > 25 mm/m² BSA (in patients with small body size) or resting LVEF ≤ 50%.</i> | I | B |
| <i>Surgery may be considered in asymptomatic patients with LVESD > 20 mm/m² BSA (especially in patients with small body size) or resting LVEF ≤ 55%, if surgery is at low risk.</i> | IIb | C |
| <i>Surgery is recommended in symptomatic and asymptomatic patients with severe aortic regurgitation undergoing CABG or surgery of the ascending aorta or of another valve.</i> | I | C |
| <i>Aortic valve repair may be considered in selected patients at experienced centres when durable results are expected.</i> | IIb | C |
| B) Aortic root or tubular ascending aortic aneurysm ⁽¹⁾ (irrespective of the severity of aortic regurgitation): | | |
| <i>Valve-sparing aortic root replacement is recommended in young patients with aortic root dilation, if performed in experienced centres and durable results are expected.</i> | I | B |
| <i>Ascending aortic surgery is recommended in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥ 50 mm.</i> | I | C |
| <i>Ascending aortic surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter:</i> | IIa | C |

(1) For clinical decision making, dimensions of the aorta should be confirmed by ECG-gated CCT.

| | | |
|--|------------|----------|
| <ul style="list-style-type: none"> ○ ≥ 55 mm in all patients. ○ ≥ 50 mm in the presence of a bicuspid valve with additional risk factors ⁽¹⁾ or coarctation. ○ ≥ 45 mm in the presence of Marfan syndrome and additional risk factors or patients with a TGFBR1 or TGFBR2 mutation (including LoeysDietz syndrome). ⁽²⁾ | | |
| When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥ 45 mm. ⁽³⁾ | IIa | C |

Patients with advanced symptoms or LV dysfunction:

- As opposed to MR, LV function does not usually deteriorate postoperatively and is likely to improve even with markedly reduced EF. In AI, the reduced EF is secondary to the high afterload rather than intrinsic dysfunction (afterload mismatch). AVR reduces regurgitant flow, which reduces LV wall stress/afterload and allows an improvement of EF, the earliest sign being a reduction of LV size.
- *No EF cutoff is prohibitive of AVR.* Patients with EF < 25% may have irreversible myocardial damage and persistent LV dysfunction postoperatively, yet most of these patients have a meaningful postoperative recovery, particularly if symptoms are class II-III, LV dysfunction is recent.

▪ **Medical therapy:**

(1) Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe AR or MR, desire for pregnancy, uncontrolled systemic hypertension and/or aortic size increase > 3 mm/year (using serial echocardiography or CMR measurements at the same level of the aorta confirmed by ECG-gated CCT).

(2) A lower threshold of 40 mm may be considered in women with low BSA, in patients with a TGFBR2 mutation or in patients with severe extra-aortic features.

(3) Considering age, BSA, aetiology of the valvular disease, presence of a bicuspid aortic valve, and intraoperative shape and thickness of the ascending aorta.

- ACEI or dihydropyridines CCBs may provide symptomatic improvement in individuals with chronic severe aortic regurgitation in whom surgery is not feasible. The value of ACEI or dihydropyridine CCBs in delaying surgery in the presence of moderate or severe AI in asymptomatic patients has not been established and their use is not recommended for this indication.
- In patients with Marfan syndrome, beta-blockers remain the mainstay for medical treatment and reducing shear stress and aortic growth rate and should be considered before and after surgery. While ARBs did not prove to have a superior effect when compared to beta-blockers, they may be considered as an alternative in patients intolerant to beta-blockers. By analogy, while there are no studies that provide supporting evidence, it is common clinical practice to advise beta-blocker or ARBs in patients with bicuspid aortic valve if the aortic root and/or ascending aorta is dilated.

N.B:

In patients with moderate aortic regurgitation who undergo CABG or mitral valve surgery, the decision to treat the aortic valve is controversial, as data show that progression of moderate aortic regurgitation is very slow in patients without aortic dilation. The Heart Team should decide based on the aetiology of aortic regurgitation, other clinical factors, the life expectancy of the patient, and the patient's operative risk. The level of physical and sports activity in the presence of a dilated aorta remains a matter of clinical judgment in the absence of evidence.

Follow-up:

- All asymptomatic patients with severe AI and normal LVEF should be followed up at least **every year**.
- In patients with either a first diagnosis or with LV diameter and/or ejection fraction showing significant changes or approaching thresholds for surgery, follow-up should be continued at 3-6 month intervals.
- Patient's BNP levels could be of potential interest as a predictor of outcomes (particularly symptom onset and deterioration of LV function) and may be helpful in the follow-up of asymptomatic patients.
- Patients with mild-to-moderate AI can be seen on a yearly basis and echocardiography performed every 2 years.

- If the ascending aorta is dilated (> 40 mm), it is recommended to perform CCT or CMR. Follow-up assessment of the aortic dimension should be performed using echocardiography and/or CMR. Any increase > 3 mm should be validated by CCT angiography/CMR and compared with baseline data.
- After repair of the ascending aorta, Marfan patients remain at risk for dissection of the residual aorta and lifelong regular multidisciplinary follow-up at an expert centre is required.
- **Pregnancy and AR:**
- Women with Marfan syndrome and an aortic diameter > 45 mm are strongly discouraged from becoming pregnant without prior repair because of the high risk of dissection.
- Although the actual risk of dissection is not well-documented in the setting of bicuspid valves, counselling against pregnancy is recommended in the setting of aortic diameters > 50 mm.

Screening:

- Given the family risk of thoracic aortic aneurysms, screening and referral for genetic testing of the patient's first-degree relatives with appropriate imaging studies is indicated in patients with connective tissue disease.
- For patients with bicuspid valves, it is appropriate to have an echocardiographic screening of first-degree relatives.

Tricuspid stenosis

- Tricuspid stenosis is often combined with tricuspid regurgitation, most frequently of **rheumatic origin**. It is therefore almost always associated with left-sided valve lesions, particularly mitral stenosis, that usually dominate the clinical presentation. Other causes are rare, including congenital, carcinoid syndrome ⁽¹⁾, drug-induced valve diseases, Whipple's disease, endocarditis and large right atrial tumour obstructing the tricuspid orifice.
- **Echocardiographic evaluation** of the anatomy of the valve and its subvalvular apparatus is important to assess valve reparability.
No generally accepted grading of tricuspid stenosis severity exists, but a mean gradient ≥ 5 mmHg at normal heart rate is considered indicative of clinically significant tricuspid stenosis.
The lack of pliable leaflet tissue is the main limitation for valve repair.
- **Medical therapy:** Diuretics are useful in the presence of HF symptoms (limited long-term efficacy).

Tricuspid regurgitation

Aetiology:

- **Secondary TR (90% of cases):** TR pressure and/or volume overload mediated RV dilatation or enlarged right atrium and tricuspid annulus due to chronic AF. Secondary TR is associated with left-sided valvular or myocardial dysfunction in most cases. It may also develop late after left-sided valve surgery.

The high RV pressure as well as the secondary RV dilatation, annular dilatation, and leaflet tethering lead to TR. As opposed to functional MR, annular dilatation is the more important factor in functional TR (the right papillary muscles are highly placed

(1) *Carcinoid heart disease is related to the secretion of serotonin by a neuroendocrine tumor (usually GI tumor). This leads to thickening of the right-sided valves, particularly the tricuspid valve.*

Since serotonin is degraded by the lungs, the left valves are not involved unless right-to-left shunt or pulmonary metastasis is present. The tricuspid leaflets become thickened and completely immobile along their entire length, with lack of opening or closure, which explains the combined stenosis and regurgitation.

and less severely tether the tricuspid leaflets). The tricuspid annulus is very dynamic and may considerably “shrink” with volume unloading.

▪ **Primary TR etiologies:**

- Rheumatic fever (one-third of rheumatic MS cases have intrinsic tricuspid involvement)
- Endocarditis (especially in intravenous drug addicts)
- Atrial fibrillation induces annular remodelling even in the absence of left-heart disease.
- Cardiac implantable electronic device-lead implantation leads to progressive tricuspid regurgitation in 20-30% of the patients and predicts its progression over time. TR may result from valve perforation but more commonly results from impingement on the leaflets or apparatus by the lead, or lead adherence to the valve. Isolated RV failure was the mode of presentation in 50% of these cases, sometimes years after device implantation.
- Flail leaflet from blunt thoracic or abdominal trauma (abdominal trauma briskly increases IVC pressure, which may rupture the tricuspid valve).
- Carcinoid syndrome, tricuspid valve prolapse, Ebstein anomaly.

N.B: Secondary TR is always associated with an elevated RA pressure and a large V wave, as, by definition, decompensated RV failure is present. Conversely, in primary TR, the RA may be highly compliant and RA pressure may be normal.

Natural history of TR:

- **A primary, severe TR** is well tolerated for months or years before it leads to RV failure, as long as the pulmonary artery pressure is normal. In fact, RV tolerates volume overload. However, TR secondary to pulmonary hypertension is not well tolerated and aggravates RV function and RV dilatation.
- **In TR secondary** to left valvular disease, percutaneous or surgical correction of the left valvular problem reduces PA pressure and may eventually reduce TR. However, *TR often does not improve*, and rather leads to more annular dilatation, TR and RV failure, particularly in patients with underlying MS or ischemic MR and a dilated tricuspid annulus > 35-40 mm on TTE (or > 21 mm/m²). Therefore, adjunctive tricuspid annuloplasty is reasonable in severe TR, or mild/moderate TR with severe annular

dilatation, and is associated with improved functional capacity and reduced long-term risk of TR and HF (yet questionable survival benefit). In general, tricuspid annuloplasty concomitant to mitral surgery does not significantly increase the surgical risk and pump time, whereas reoperation for severe progressive TR after mitral surgery is associated with a high mortality of 10-25%, further justifying concomitant surgery.

Evaluation:

- In primary TR, specific abnormalities of the valve can be identified. In secondary TR, annular dilatation, along with RV and RA dimensions, as well as RV function should be measured, owing to their prognostic relevance.
 - PA pressure > 55 mmHg **or** PVR > 3 WU implies that TR is secondary to pulmonary hypertension.
 - PA pressure < 40-50 mmHg with normal PVR favors either primary TR **or** TR secondary to a pure RV volume overload (ASD, ARVD).
- Importantly, estimation of pulmonary pressures using Doppler gradient may be impossible or might underestimate the severity of pulmonary hypertension in the presence of severe tricuspid regurgitation, justifying cardiac catheterization to evaluate pulmonary vascular resistances.

| Table 11-17: Echocardiographic criteria for grading severity of tricuspid regurgitation | |
|---|--|
| Qualitative | |
| Tricuspid valve morphology | <i>Abnormal/flail</i> |
| Colour flow regurgitant jet | <i>Very large central jet or eccentric wall impinging jet ⁽¹⁾</i> |
| CW signal of regurgitant jet | <i>Dense/triangular with early peaking</i> |
| Semiquantitative | |
| Vena contracta width (mm) | <i>> 7 ⁽²⁾</i> |

(1) At a Nyquist limit of 50-60 cm/s.
 (2) At a Nyquist limit of 50-60 cm/s .. Preferably biplane.

| | |
|--|---|
| PISA radius (mm) | > 9 ⁽¹⁾ |
| Hepatic vein flow | <i>Systolic flow reversal</i> |
| Tricuspid inflow | <i>E-wave dominant ≥ 1 m/s</i> ⁽²⁾ |
| Quantitative | |
| EROA (mm²) | ≥ 40 |
| Regurgitant volume (mL/beat) | ≥ 45 |
| Enlargement of cardiac chambers/vessels | <i>RV, RA, inferior vena cava</i> |

(1) Baseline Nyquist limit shift of 28 cm/s

(2) In the absence of other causes of elevated RA pressure.

Management:

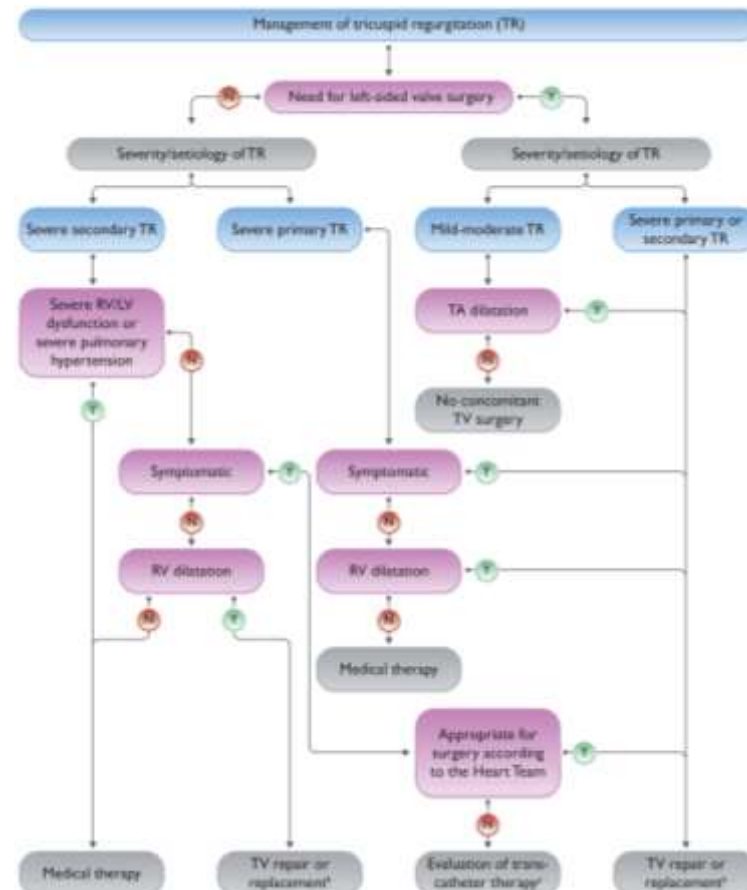


Figure 11-15: Management of tricuspid regurgitation. A) The Heart Team with expertise in the treatment of tricuspid valve disease evaluates anatomical eligibility for transcatheter therapy including jet location, coaptation gap, leaflet tethering, potential interference with pacing lead. B) Replacement when repair is not feasible. **Source:** 2021 ESC/EACTS Guidelines for

▪ **Medical therapy:**

Diuretics are useful in the presence of right heart failure. To counterbalance the activation of the renin angiotensin-aldosterone system associated with hepatic congestion, the addition of an aldosterone antagonist may be considered.

Although data are limited, rhythm control may help to decrease tricuspid regurgitation and contain annular dilatation in patients with chronic AF. Importantly, in the absence of advanced RV dysfunction or severe pulmonary hypertension, none of the above-mentioned therapies should delay referral for surgery or transcatheter therapy.

▪ **Indications for intervention:**

| Table 11-18: ESC Recommendations on indications for intervention in tricuspid valve disease: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Tricuspid stenosis: | | |
| <i>Surgery is recommended in patients with severe tricuspid stenosis if symptomatic ⁽¹⁾ or undergoing left-sided valve intervention ⁽²⁾.</i> | I | C |
| Primary tricuspid regurgitation: | | |
| <i>Surgery is recommended in patients with:</i> <ul style="list-style-type: none"> ○ Severe primary TR undergoing left sided valve surgery. ○ Symptomatic patients with isolated severe primary TR without severe RV dysfunction. | I | C |
| <i>Surgery should be considered in patients with:</i> <ul style="list-style-type: none"> ○ moderate primary TR undergoing left-sided valve surgery. ○ asymptomatic or mildly symptomatic patients with isolated severe primary TR and RV dilatation who are appropriate for surgery. | IIa | C |
| Secondary tricuspid regurgitation: | | |

(1) Percutaneous balloon valvuloplasty can be attempted as a first approach if tricuspid stenosis is isolated.

(2) Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve.

| | | |
|--|------------|----------|
| <i>Surgery is recommended in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery.</i> | I | B |
| <i>Surgery should be considered in patients with:</i> <ul style="list-style-type: none"> ○ <i>Mild or moderate secondary TR with a dilated annulus (≥ 40 mm or > 21 mm/m² by 2D echocardiography) undergoing left-sided valve surgery.</i> ○ <i>Severe secondary TR (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular hypertension ⁽¹⁾.</i> | IIa | B |
| <i>Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease ⁽²⁾.</i> | IIb | C |

Surgical approaches:

- Tricuspid annuloplasty is preferred to replacement. There are two types of tricuspid annuloplasty: (1) ring annuloplasty; (2) suture annuloplasty, which consists of a single suture tied circumferentially around the posterior and anterior aspects of the annulus (de Vega).
A ring has more sustained long-term efficacy than a suture, lasting > 5 years, but requires more surgical time (~30 minutes). De Vega annuloplasty usually requires < 5 minutes and does not significantly add to the operative ischemic time.
- A bioprosthesis is preferred to a mechanical prosthesis because of the high thrombotic risk on the right side, where the closing pressure is low. Also, a bioprosthetic valve lasts longer in a low-pressure system (i.e., tricuspid, or, even better, pulmonic position).

(1) *In patients with previous surgery, recurrent left-sided valve dysfunction needs to be excluded.*

(2) *Transcatheter treatment can be performed according to Heart Team at experienced valve centres in anatomically eligible patients in whom improvement of quality of life or survival can be expected.*

Pulmonic Stenosis (PS)

Aetiology:

- PS is usually congenital. While the normal pulmonic valve is tricuspid, the stenotic pulmonic valve is a domed valve with extensive commissural fusions, leading to an acommisural morphology with a small central orifice (no commissure, or one or two commissures). Rarely, the valve is tricuspid with diffuse myxomatous thickening and little or no commissural fusion (dysplastic valve, e.g., Noonan's syndrome).
- Other causes of PS: rheumatic, carcinoid (always in conjunction with other valvular diseases).

Natural history:

- Pulmonic stenosis leads to RV hypertrophy but not RV dilatation and failure. In fact, RA pressure is characterized by a large A wave but a normal V wave. The congenital RV maintains its function for years even when the RV pressure is in the systemic range; thus, in RV failure, one should look for an associated "volume" lesion such as ASD, TR, or PR.
- Usually in PS, RV does not fail until later in life (fifth decade) unless atrial arrhythmias develop.
- Most patients with moderate PS eventually develop symptoms after 25 years and require valvotomy ⁽¹⁾.

Evaluation:

- PS is considered severe when the peak-to-peak gradient is ≥ 64 mmHg. The gradient in PS, particularly mild or moderate PS, usually remains stable over the long-term follow-up. Severe PS is usually symptomatic and is treated with percutaneous balloon valvotomy with excellent long-term result (no recurrence over > 20 years follow-up).
- On chest X-ray, PS is characterized by a dilated main and left pulmonary arteries (post stenotic dilatation). As opposed to Eisenmenger syndrome, the lung perfusion is normal (no oligemia).

(1) Dysplastic PS does not respond to valvuloplasty, as the primary process is not commissural fusion.

Treatment:

Percutaneous valvotomy is indicated for PS with a peak-to-peak gradient ≥ 64 mmHg.

Patients with PS have a hypertrophied RVOT. Following percutaneous valvuloplasty, the reduction in RV afterload reduces RV volume and may cause a dynamic obstruction across the hypertrophied RVOT and a residual gradient that is actually an intraventricular gradient. The RVOT obstruction may be severe (“suicide RV”) and is initially treated with fluids, β -blockers, and CCBs. This gradient resolves gradually.

Pulmonic Regurgitation (PR)

- **Secondary PR:** The most common cause of PR is pulmonary hypertension, classically seen with MS.
- **Primary PR** may be seen decades after surgical therapy of tetralogy of Fallot, valvotomy for PS, or after Ross procedure. It may also be seen with endocarditis and carcinoid syndrome.
 - When associated with pulmonary hypertension, PR leads to Graham Steell’s PR murmur, which is a diastolic murmur similar to AI, except that it is heard at the left second intercostal space and increases with inspiration.
 - Valve replacement may be required for severe PR related to endocarditis or surgical correction of tetralogy of Fallot if *symptomatic RV failure* ensues. RV size tends to normalize and functional status improves when pulmonic valve replacement is performed for PR late after tetralogy of Fallot repair. However, RV function may not fully recover once marked enlargement and systolic dysfunction are evident. Therefore, many experts recommend valve replacement in asymptomatic severe PR with RV dilatation/dysfunction.

Mixed Valvular Lesions

Significant stenosis and regurgitation can be found on the same valve. Disease of multiple valves may be encountered in several conditions, particularly in rheumatic and congenital heart disease, but also less frequently in degenerative valve disease.

Mixed Single-Valve disease:

- When either stenosis or regurgitation is predominant, management follows the recommendations concerning the predominant VHD.
- When the severity of both stenosis and regurgitation is balanced, indications for interventions should be based on symptoms and objective consequences rather than on the indices of severity of stenosis or regurgitation. In this setting, Doppler pressure gradient reflects the global haemodynamic burden (stenosis and regurgitation) of the valve lesion.

Since the flow across the valve is increased, the transvalvular gradient is increased in comparison to valvular stenosis without regurgitation. This leads to overestimation of the anatomic severity of the stenosis when assessed by gradient. *The gradient, however, correlates with the physiologic consequences of the mixed stenosis-regurgitation and properly correlates with the overall disease severity.* The valvular area is unchanged when calculated by Doppler echo (continuity equation for AS or MS, or pressure half-time for MS).

Multiple Valvular Involvement:

The clinical effect of the proximal lesion is more prominent than that of the distal lesion. *The proximal lesion tends to mask the severity of the more distal lesion by reducing the flow across the distal lesion, whereas the distal lesion tends to exacerbate the hemodynamic effect of the proximal lesion because of increased backward volume and/or pressure.*

- In **severe MR or MS associated with AS**:
 - AS worsens the hemodynamic effects of MS or MR and may worsen the severity of MR (from moderate to severe). In combined AS and MR, the LV is exposed to both pressure and volume overload in systole.
 - Aortic stenosis does not affect the assessment of severity of mitral valve disease, except that MVA may be falsely increased when calculated using the echocardiographic pressure half-time.
 - On the other hand, the severity of AS may be underestimated by gradient assessment as a result of the low cardiac output, but may be overestimated by AVA assessment (low-flow/low-gradient pseudo-severe AS).

- If surgery is indicated for the mitral valve, consider anatomic assessment of the severity of AS during surgery (palpation of the aortic valve) to make a decision about concomitant aortic valve replacement.
- When MS is associated with mild AS and PMC is planned, reassess the aortic valve after treatment of MS.
- In **severe MS with AI**:
 - the hemodynamic effect of MS is exacerbated. The patient has a higher LA pressure than a patient with isolated MS, but less LV dilatation and less elevated LVEDP than a patient with isolated AI.
 - The severity assessment of MS or AI by catheterization and of AI by echo Doppler are not affected; MVA calculated by Doppler pressure half-time is falsely increased.
- **Combined MR-AI is the most poorly tolerated combination.** The LV gets a double volume load in diastole and is more severely enlarged than with either lesion alone. MR is aggravated, and the regurgitant MR volume is more severely increased than with isolated MR. LV and LA filling pressures and volumes are more severely increased than with each lesion alone. The combination does not affect the echocardiographic or invasive assessment of either lesion. MR may be functional, secondary to LV dilatation; AVR alone often improves functional MR, but MV annuloplasty is usually warranted.

Prosthetic valves

Types of prosthetic valve:

On the basis of the leaflet material, Two different types of surgical prosthetic heart valves exist:

- **A mechanical valve** may be bileaflet (e.g., St Jude, Carbomedics) or single tilting disk (Medtronic-Hall).
- **A bioprosthesis** can be:
 - **Stented**: a porcine trileaflet valve **or** a bovine pericardial trileaflet valve, with three components: ring, struts (both mounted over a stent frame), and leaflets arising from the struts. The leaflets, per se, do not contain any metal.
 - **Stentless**: are less commonly used, may be porcine or homograft valves. They have a thin ring and thin struts and are only available for the aortic position. These stentless valves provide greater effective orifice areas and lower transprosthetic

gradients than stented prosthetic valves. The modern stentless bioprotheses (e.g., Freestyle) have excellent mid-term but unclear long-term durability.

- **Percutaneous:** the percutaneous aortic prosthesis consists of leaflets mounted inside a thin stent frame without bulky struts; the leaflets are stentless.

Selection of prosthetic valve:

Mechanical valves are more durable, yet more thrombogenic. Conversely, Bioprosthetic valves are less thrombogenic and less durable, but exhibit more natural hemodynamic properties.

- **Regarding age:**
 - For mitral valve: - Age < 65 years → mechanical prosthesis - Age ≥ 70 years → bioprosthesis
 - For aortic valve: - Age < 60 years → mechanical prosthesis - Age ≥ 65 years → bioprosthesis.
- In aortic valve endocarditis, a homograft is preferred (as it allows antibiotic penetration).
- In case of a small scarred annulus, the lowest profile valves ⁽¹⁾ are the best option: TAVR or stentless bioprosthesis (e.g., Freestyle).

(1) The term “profile” refers to the height from the base of the prosthesis to the top of the struts. The introduction of low-profile valves reduced the “mass to orifice ratio,” thereby improving hemodynamics. The stentless bioprosthesis, the TAVR bioprosthesis, and the bileaflet mechanical valve have the lowest profile (i.e., the largest orifice area and lowest gradient for the same ring size).

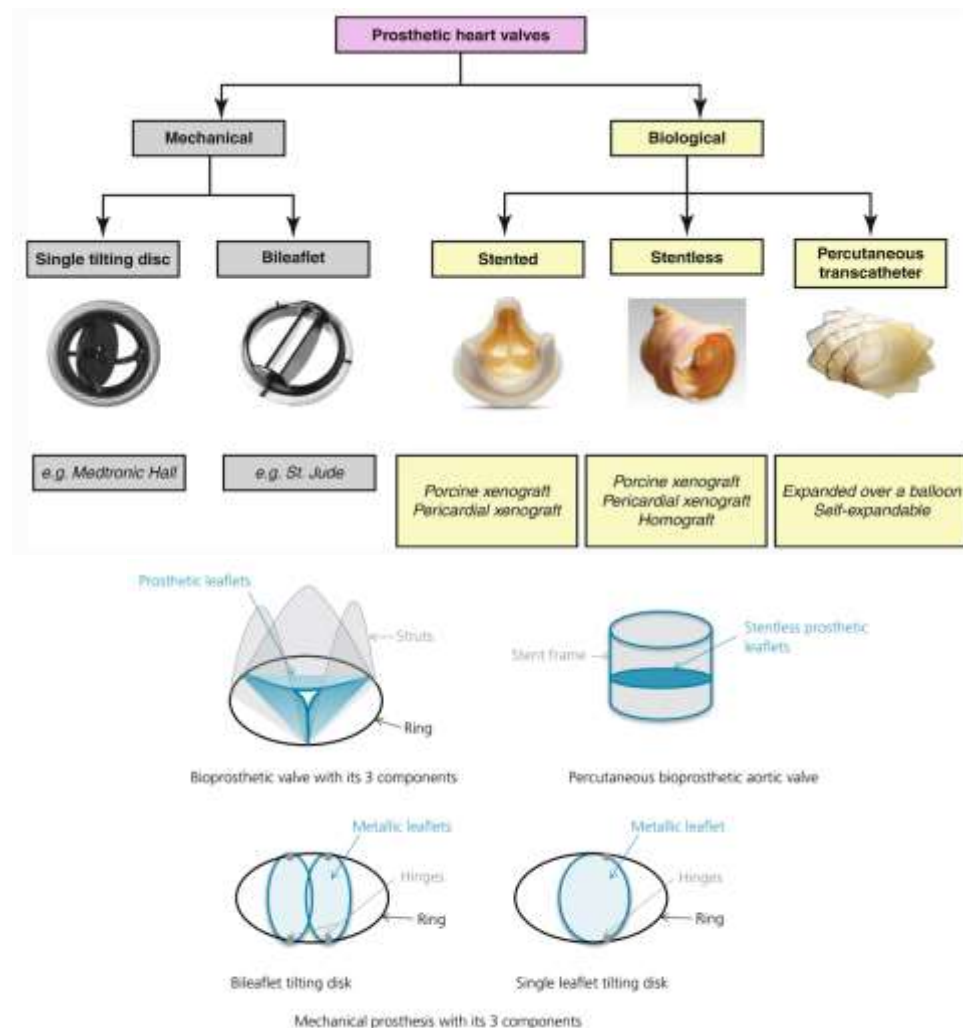


Figure 11-16: Prosthetic valves. Surgical bioprostheses typically have a metallic stent frame that extends from the sewing ring to each strut. Stentless bioprostheses have very thin rings and struts without any metal.
Source: Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Table 11-19: ESC Recommendations for prosthetic valve selection:

| Recommendations | Class | Level |
|---|---------------------------|--------------|
| Mechanical prostheses: | | |
| <i>A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to longterm anticoagulation ⁽¹⁾.</i> | I | C |
| <i>A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration ⁽²⁾.</i> | I | C |
| <i>A mechanical prosthesis should be considered in:</i> | | |
| - <i>Patients already on anticoagulation because of a mechanical prosthesis in another valve position.</i> | IIa | C |
| - <i>Patients aged < 60 years for prostheses in the aortic position and aged < 65 years for prostheses in the mitral position ⁽³⁾.</i> | IIa | B |
| - <i>Patients with a reasonable life expectancy for whom future redo valve surgery or TAVI (if appropriate) would be at high risk.</i> | IIa | C |
| <i>A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism ⁽⁴⁾.</i> | IIb ⁽⁵⁾ | C |
| Biological prostheses: | | |
| <i>A bioprosthesis is recommended according to the desire of the informed patient.</i> | I | C |

(1) Increased bleeding risk because of comorbidities, adherence concerns or geographic, lifestyle or occupational conditions.

(2) Young age (< 40 years), hyperparathyroidism, haemodialysis.

(3) In patients 60-65 years of age who should receive an aortic prosthesis and those between 65 and 70 years of age in the case of mitral prosthesis, both valves are acceptable, and the choice requires careful analysis of factors other than age.

(4) Risk factors for thromboembolism are AF, previous unprovoked proximal deep venous thromboembolism and/or symptomatic pulmonary embolism, hypercoagulable state, antiphospholipid antibody.

(5) This weak recommendation is stated as interruption of anticoagulation is far less risky in AF compared to mechanical prosthesis, and NOAC is an option in AF patients receiving a bioprosthesis (vs. warfarin in mechanical prosthesis).

| | | |
|--|------------|----------|
| <i>A bioprosthesis is recommended when good quality anticoagulation is unlikely, contraindicated because of high bleeding risk and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis ⁽¹⁾.</i> | I | C |
| <i>A bioprosthesis is recommended in case of reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.</i> | I | C |
| <i>A bioprosthesis should be considered in:</i> <ul style="list-style-type: none"> - Patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery. - Young women contemplating pregnancy. - Patients aged > 65 years for a prosthesis in the aortic position or aged > 70 years in a mitral position. | IIa | C |
| <i>A bioprosthesis may be considered in patients already on long-term NOACs due to the high risk for thromboembolism.</i> | IIb | B |

Management after valve intervention:

▪ Echocardiographic follow-up:

- **Postoperative period:** echo should be performed **6 weeks** postoperatively to obtain baseline function and gradient across the prosthesis. This baseline gradient provides a reference in case of any future deterioration.
Follow-up echo is indicated at **6-12 months** in patients with severe LV dysfunction to assess for improvement in LV size and function. Otherwise, echo is only indicated if there is a change in symptoms.
- **After mechanical valves:** Routine echo is not indicated, not even years after valve replacement.
- **After Bioprosthetic valves:** Conversely, yearly echo surveillance is reasonable after 10 years, or 5 years in young patients, to detect severe deterioration early on before LV dysfunction or HF occurs.
- **After TAVR,** more stringent echo surveillance is recommended: before discharge, at 30 days, then yearly.

(1) Life expectancy should be estimated at > 10 years according to age, sex, comorbidities, and country-specific life expectancy.

- **After mitral valve repair**, echo is recommended at 1 year then every 2-3 years.
- **Antithrombotic management:**
- **Target INR:** Prosthetic valve thrombosis depends on **valvular closing pressure**. The low closing pressure on the right side explains the high thrombotic risk of prosthetic valves in this position. Despite a higher closing pressure, the mitral valve has a higher thrombotic risk than the aortic valve, because of its proximity to the diseased, sluggish LA, prone to microthrombus formation.

| Table 11-20: Target INR for mechanical prostheses: | | |
|---|--|-------------------------|
| Prosthesis thrombogenicity | Patient-related risk factors ⁽¹⁾ | |
| | None | ≥ 1 risk factors |
| Low ⁽²⁾ | 2.5 | 3.0 |
| Medium ⁽³⁾ | 3.0 | 3.5 |
| High ⁽⁴⁾ | 3.5 | 4.0 |

(1) Mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis of any degree, LVEF < 35%.

(2) Carbomedics, Metronic Hall, ATS, Medtronic Open-Pivot, St Jude medical, On-X, Sorin Bicarbo.

(3) Other bileaflet valves with insufficient data.

(4) Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves

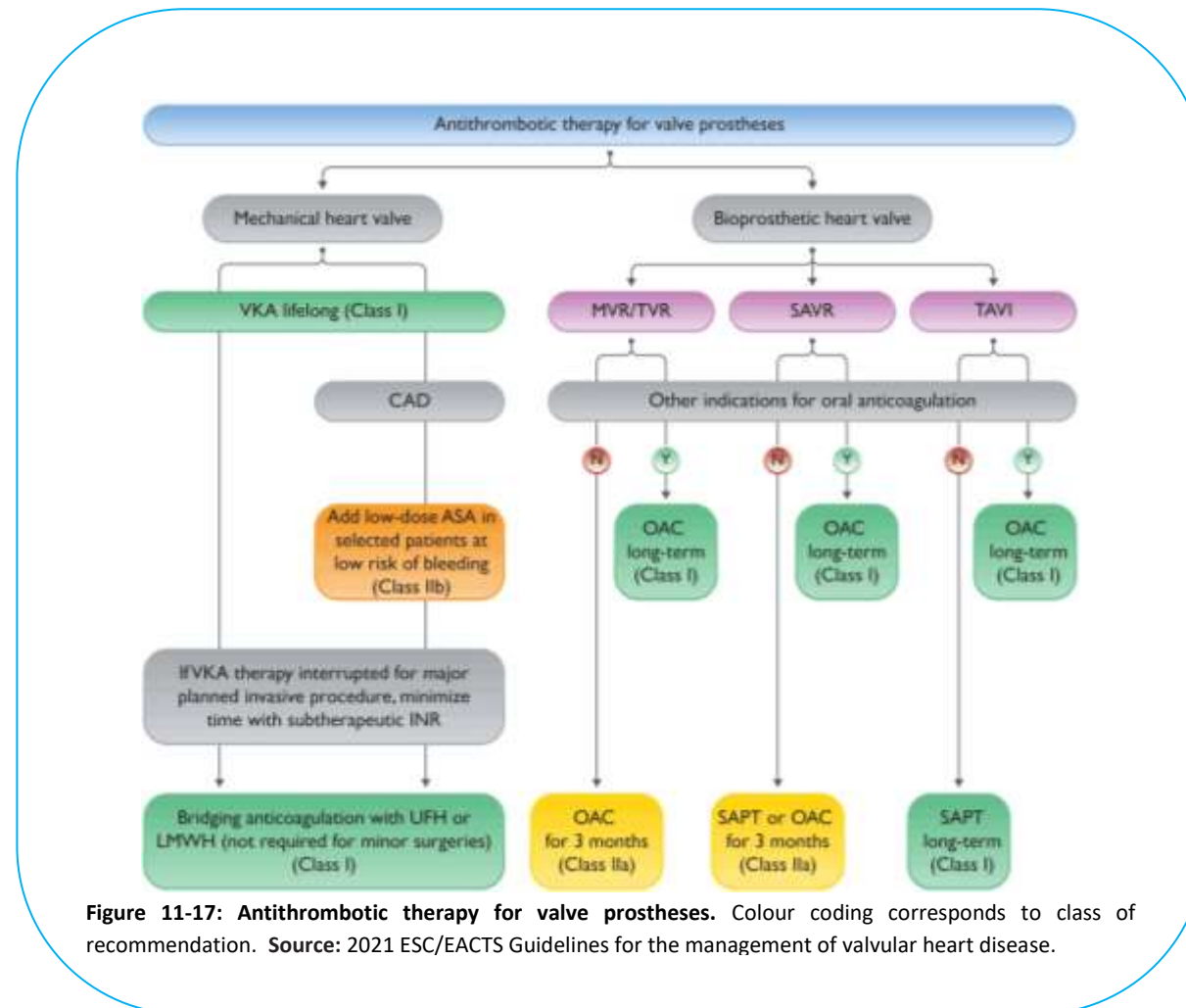


Figure 11-17: Antithrombotic therapy for valve prostheses. Colour coding corresponds to class of recommendation. Source: 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

- **Management of VKA overdose and bleeding:**

- **In case of major bleeding or urgent surgery:** VKA should be discontinued, and 10 mg vitamin K should be administered by slow i.v. infusion and repeated every 12 h if needed.

Until the anticoagulation effect is reversed, administration of prothrombin complex concentrate (PCC) and/or fresh frozen plasma (FFP) should be initiated according to body weight and pre-treatment INR. The efficacy should be monitored by recheck of INR at 30 min and every 4-6 h until normalization.

The optimal time to restart anticoagulation should be discussed in relation to location of the bleeding event and interventions performed to stop bleeding and/or to treat an underlying cause.

- **In asymptomatic patients with INR > 10:** VKA must be stopped, and oral vitamin K (2.5-5 mg) prescribed, while the INR must be monitored on a daily base for 2 weeks.
- **In patients with INR between 4.5 and 10:** warfarin should be stopped temporarily, and a small dose of oral vitamin K (1-2 mg) can be considered on an individual basis balancing between the risks ⁽¹⁾.
- **In asymptomatic patients with INR < 4.5** require careful down-titration and/or skipping one or more doses.
- In all patients with MHVs, VKAs must be resumed once the INR achieves the therapeutic range or is slightly elevated.

- **Interruption of VKA for planned invasive procedures:**

- **Minor surgical procedures:** It is recommended not to interrupt oral anticoagulation.
- **Major surgical procedures** require an INR < 1.5. Oral anticoagulant therapy should be stopped before surgery and bridging using heparin is recommended when INR falls below 2 (typically 36-48 hours after warfarin discontinuation).
- UFH remains the only approved heparin treatment in patients with mechanical prostheses; IV administration should be favoured over the SC route.
- The use of subcutaneous LMWH, although off-label, is an alternative to UFH for bridging. When LMWHs are used they should be administered twice a day using therapeutic doses, adapted to body weight and renal function and, if possible, with monitoring of anti-Xa activity with a target of 0.5-1.0 U/mL.

(1) multiple RCTs suggest no difference in bleeding events with vitamin K vs. placebo.

- Fondaparinux should not be used for bridging in patients with mechanical prosthesis.

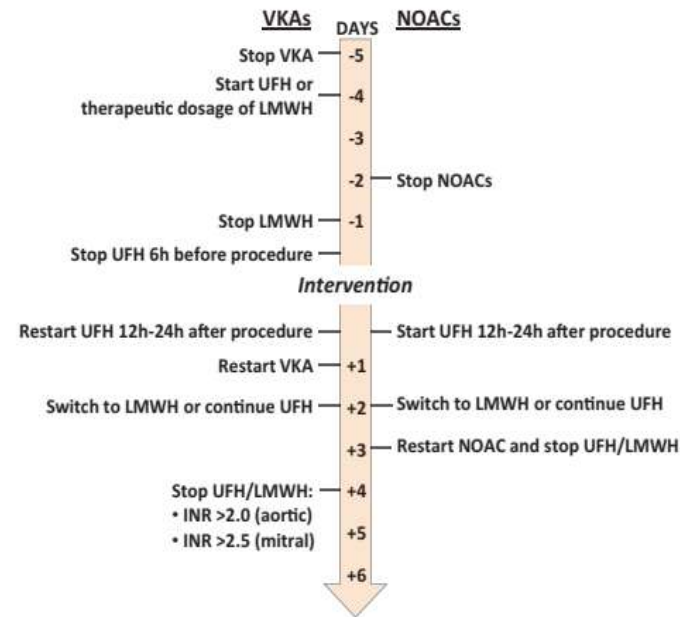


Figure 11-18: Management of OAC in patients with an indication for preoperative bridging. Source: 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery.

N.B: In patients who have a subtherapeutic INR during routine monitoring, bridging with UFH or preferably LMWH in an outpatient setting is indicated until a therapeutic INR value is reached.

Table 12-21: ESC Recommendations for management of antithrombotic therapy after prosthetic valve implantation or valve repair in the perioperative and postoperative periods:

| Recommendations | Class | Level |
|--|------------|----------|
| Surgical valve replacement: | | |
| <i>OAC using a VKA is recommended lifelong for all patients with an MHV prosthesis.</i> | I | B |
| <i>For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.</i> | I | B |
| <i>OAC is recommended for patients undergoing implantation of a surgical BHV who have other indications for anticoagulation ⁽¹⁾.</i> | I | C |
| <i>In patients with no baseline indications for OAC,</i> <ul style="list-style-type: none"> <i>- OAC using a VKA should be considered for the first 3 months after surgical implantation of a bioprosthesis in the mitral or tricuspid position. (until the sewing cuff endothelializes)</i> <i>- low-dose aspirin (75-100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV.</i> | IIa | B |
| <i>The addition of low-dose aspirin (75-100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.</i> | IIa | C |
| <i>NOACs should be considered over VKA after 3 months following surgical implantation of a BHV in patients with AF.</i> | IIa | B |
| <i>The addition of low-dose aspirin (75-100 mg/day) to VKA may be considered in selected patients with MHVs in case of concomitant atherosclerotic disease and low risk of bleeding.</i> | IIb | C |
| <i>NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF.</i> | IIb | C |

(1) e.g., LV apex thrombus, antithrombin 3 deficit and proteins C and/or S deficit

| | | |
|--|-----|---|
| NOACs are not recommended in patients with a mechanical valve prosthesis ⁽¹⁾ . | III | B |
| Surgical valve repair: | | |
| OAC with VKA should be considered during the first 3 months after mitral and tricuspid repair. | Ila | C |
| SAPT with low-dose ASA (75-100 mg/day) should be considered for the first 3 months after valve-sparing aortic surgery when there are no other baseline indications to OAC. | Ila | C |
| Transcatheter aortic valve implantation: | | |
| OAC is recommended lifelong for TAVI patients who have other indications for OAC. | I | B |
| Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC. | I | A |
| Routine use OAC is not recommended after TAVI in patients with no baseline indication for OAC. | III | B |
| Patients with an indication to concomitant antiplatelet therapy: | | |
| After uncomplicated PCI or ACS in patients requiring long-term OAC, early cessation (≤ 1 week) of aspirin and continuation of dual therapy with OAC and a P2Y ₁₂ inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used. | I | B |
| After uncomplicated PCI or ACS in patients requiring both OAC and antiplatelet therapy, triple therapy with aspirin, clopidogrel and OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the risk of bleeding, with the total duration (≤ 1 month) decided according to assessment of these risks and clearly specified at hospital discharge. | Ila | C |
| Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months. | I | B |

(1) Dabigatran has been studied with mechanical prosthetic valves (RE-ALIGN study) and was associated with a drastic increase in thromboembolic events (5% at 3 months). In fact, an overwhelming activation of the factor VII pathway, after contact with tissue factor expressed at the site of tissue or endothelial injury, may generate more thrombin than dabigatran can inhibit; warfarin may be more effective, as it blocks factor VII activation, in addition to the intrinsic (factor IX) and common pathways (factor X and thrombin).

On the other hand, RIVER trial proved the efficacy of rivaroxaban in AF with mitral bioprosthesis.

| | | |
|--|------------|----------|
| <i>In patients treated with a VKA (e.g., MHVs), clopidogrel alone should be considered in selected patients (e.g., HAS-BLED ≥ 3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months.</i> | Ila | B |
| <i>In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be considered and carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range > 65-70%.</i> | Ila | B |
| Management of antithrombotic therapy in the perioperative period: | | |
| <i>It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR < 1.5 ⁽¹⁾.</i> | I | C |
| <i>Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indications:</i> <ul style="list-style-type: none"> • Mechanical prosthetic heart valve. • AF with significant mitral stenosis. • AF with a CHA₂DS₂-VASc score ≥ 3 for women or 2 for men. • Acute thrombotic event within the previous 4 weeks. • High acute thromboembolic risk ⁽²⁾. | I | C |
| <i>Therapeutic doses of either UFH or subcutaneous LMWH are recommended for bridging.</i> | I | B |
| <i>In patients with MHVs, it is recommended to (re)- initiate the VKA on the first postoperative day.</i> | I | C |
| <i>In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 h after surgery.</i> | I | C |
| <i>In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period.</i> | I | C |

(1) ≤ 5 days for warfarin and ≤ 3 days for acenocoumarol.

(2) LV apex thrombus, antithrombin III deficit and proteins C and/or S deficit.

| | | |
|--|------------|----------|
| <i>In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery in the absence of an indication for OAC, it is recommended to resume the P2Y12 inhibitor postoperatively, as soon as there is no concern over bleeding.</i> | I | C |
| <i>In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery in the absence of an indication for OAC, bridging P2Y12 inhibitors with short acting glycoprotein IIb/IIIa inhibitors or cangrelor may be considered.</i> | IIb | C |

Complications: (Rate ~2–3 % per year)

1. Degeneration:

- One-third of bioprostheses degenerate in 10-15 years. Calcification and tears/perforations occur over time. Leaflet fibrosis and calcification may lead to stenosis but also regurgitation from leaflet retraction. Cuspal tears and perforations lead to regurgitation.
- Bioprosthetic valve degeneration depends on:
 - **Cardiac output:** the higher stroke volume (e.g., young active patient, hyperthyroidism, hemodialysis) is associated with faster degeneration; also, the higher heart rate means more frequent opening and closing of the valve, and thus more injury.
 - **Valvular closing pressure:** The mitral valve degenerates faster due to high closing pressure, followed by the aortic valve, then the right-sided valves ⁽¹⁾. A bioprosthesis is often long-lasting in the right-sided position.
- Reoperation is necessary once symptoms develop, or even in asymptomatic patients with severe regurgitant or stenotic dysfunction. In fact, the risk associated with reoperation in a stable patient is only slightly higher than the risk of the first operation. Treating bioprosthetic aortic valve failure by transcatheter valve-in-valve implantation has been shown to be feasible alternative in high-risk patients.

(1) Valvular closing pressure is the difference between LV systolic pressure (e.g., 130 mmHg) and LA pressure (e.g., 10) for the mitral valve, **or** the difference between aortic diastolic pressure (e.g., 80) and LV diastolic pressure (e.g., 10) for the aortic valve.

2. Prosthetic valve thromboembolism and thrombosis:

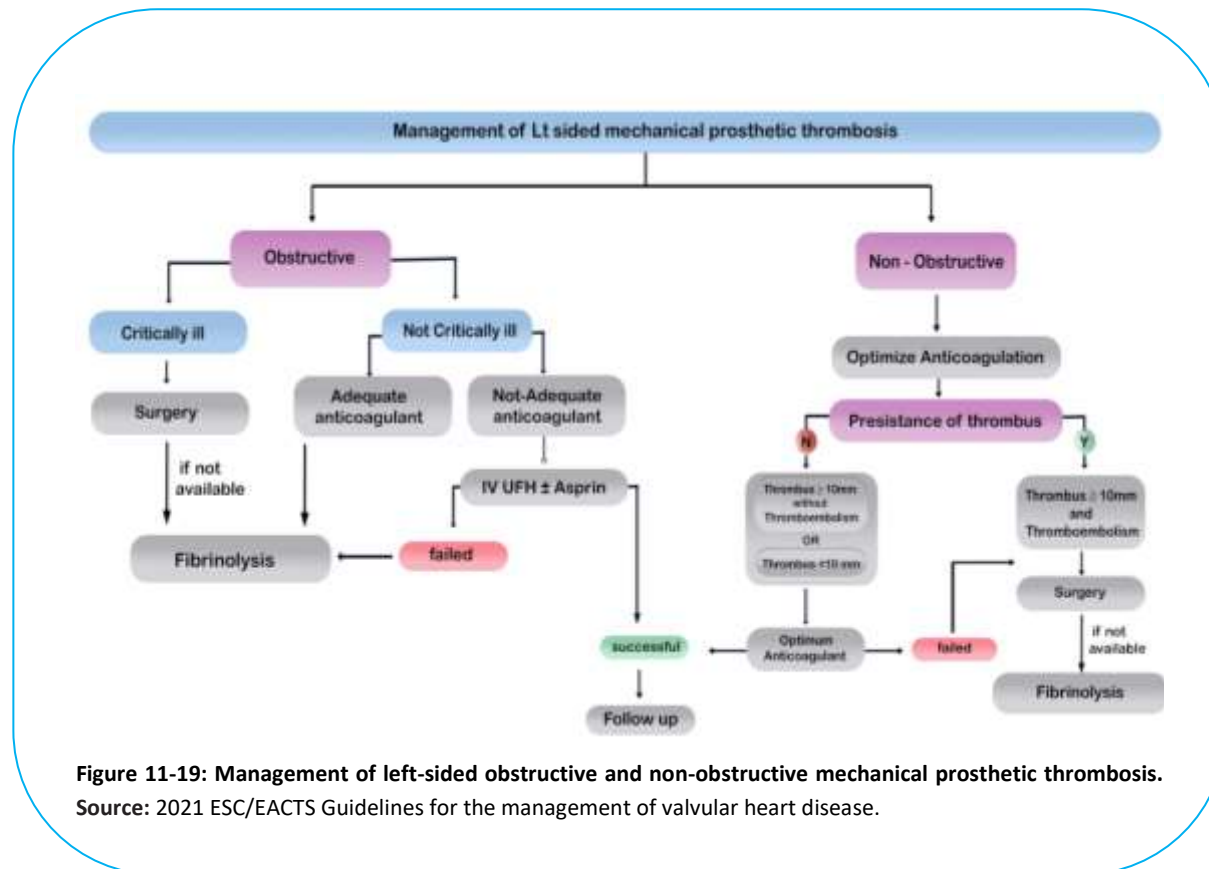
- **Thromboembolic events:** without anticoagulation, the risk of thromboembolic events with a mechanical prosthesis is 8% per year, but up to 20% in the highest-risk patient, e.g., MVR with AF or history of embolic events. Anticoagulation reduces the risk to 1-2% per year. Many thromboembolic events are due to an intermittently subtherapeutic INR, but some of them occur despite a therapeutic INR.
- **Prosthetic Valve thrombosis:** (0.1-5.7% per year): A reduced or absent leaflet motion coupled with twice as high transvalvular gradient as that given for normal prosthetic model is the hallmark of prosthetic valve thrombosis.
- The risk of PV thrombosis and TE events is higher with MHVs than with BHVs, higher for PVs implanted in the mitral position versus the aortic position, and higher for right-sided PVs than left-sided PVs.
- PV thrombosis is a complex multifactorial phenomenon, occurs due to:
 - Surface Factors: e.g., incomplete prosthesis endothelialization, malpositioning, or leaflet damage.
 - Hemodynamic Factors: e.g., Low cardiac output, prosthetic hemodynamic profile, or hyperviscosity.
 - Hemostatic Factors: e.g., hypercoagulable state, significant tissue injury.

3. Mechanical valve obstruction: (~ 0.5 % per year)

- It presents with HF, hemodynamic compromise and loss of the prosthetic click on exam.
- **Causes:** (all these processes may also be seen with a bioprosthetic valve, at a lower frequency)
 - Pannus formation: fibrosis that grows from the endocardium surrounding the sewing ring and extends onto the prosthesis.
 - Thrombosis (more common than pannus formation).
 - Early postoperative prosthetic obstruction may be due to severe annular calcification.

Table 11-22: Characteristics of Prosthetic Valve Thrombosis Versus Fibrotic Pannus:

| | PV Thrombosis | Fibrotic Pannus |
|--------------------------|---|--|
| Pathogenesis | Platelet aggregation and deposition, thrombin generation and clot formation | Thrombin generation and fibrin deposition Fibroblast proliferation, collagen deposition, and neoangiogenesis |
| Clinical features | Shorter time from valve replacement to dysfunction (weeks to months) Sudden onset of symptoms or subclinical More commonly associated with suboptimal anticoagulation | Longer time from valve replacement to dysfunction (months to years) Progressive onset of symptoms or subclinical Less commonly associated with suboptimal anticoagulation |
| Imaging | Higher total mass volume and area Higher lesion density More commonly located on the atrial side for mitral prostheses and on the aortic side for aortic prostheses Greater leaflet motion restriction | Lower total mass volume and area Lower lesion density More commonly located on the ventricular side for both mitral and aortic prostheses Less leaflet motion restriction |



4. Paraprosthetic leak:

- A paraprosthetic leak is observed with both mechanical and bioprosthetic valves.
- It is frequently due to endocarditis. It may also be due to loose sutures, or heavy annular calcium that prevents complete prosthetic apposition and suturing or leads to late suture dehiscence.
- Small, asymptomatic leaks are common early postoperatively (10-25%) and are seen on postoperative TEE. Those decrease or resolve in the ensuing days or months with the healing process.

- Valvular dehiscence is an extreme form of paravalvular leak that involves > 20-40% of the sewing ring circumference and is often due to endocarditis. It manifests as a “rocking” movement of the prosthesis on echo and fluoroscopy.
- It may cause severe regurgitation and hemolysis. Severe hemolysis may be seen with large paravalvular leaks but also with central leaks of degenerated bioprostheses. Iron replacement may be effective.
- Repair of the paraprosthetic leak with additional sutures or valvular re-replacement is indicated for a severe leak associated with HF or severe hemolysis requiring repeated transfusion (fortunately, the leak and the chronic hemolysis are often mild). A severe paravalvular leak without clear HF or symptoms does not, per se, have a clear indication for repair.

5. Endocarditis: (~ 0.5 % per year, the frequency being highest in the first 6-12 months)

- o **Early endocarditis** (< 1 year postoperatively): it is usually a complication of valve surgery, may be *Staph. coagulase*-negative and -positive. Second in frequency are enterococcal and gram-negative infections.
- o **Late endocarditis** (> 1 year postoperatively): the microbiology resembles that of native valve endocarditis. *Streptococcus* species (*viridians*, *bovis*) are the most common, followed by staphylococci and enterococci. Coagulase-negative staphylococcus may still be seen, especially after central line placement.

6. Patient/Prosthesis Mismatch (PPM):

- o PPM is defined as an indexed prosthetic effective orifice area (EOA) $\leq 0.85 \text{ cm}^2/\text{m}^2$ in the aortic position and $\leq 1.2 \text{ cm}^2/\text{m}^2$ in the mitral position. PPM is considered severe when aortic EOA is $\leq 0.75 \text{ cm}^2/\text{m}^2$, and mitral EOA $\leq 0.9 \text{ cm}^2/\text{m}^2$.
- o $\text{EOA}_{\text{Pr}} = \text{CSA}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{Pr}}$ Indexed EOA = EOA of prosthesis/patient's BSA
- o PPM occurs more commonly in patients with a small scarred mitral or aortic annulus, forcing the surgeon to place a small prosthesis. This is more likely to occur with valvular replacement performed for aortic or mitral stenosis rather than regurgitation, as the annulus is usually scarred in these cases.

- TAVR is associated with a lower prevalence of PPM, especially severe PPM, compared with surgical AVR. Among transcatheter valves, self-expanding valves with supra-annular design are generally associated with a lower prevalence of PPM compared with balloon-expandable valves.
- **Clinical Sequelae of PPM:** PPM has a particular impact on young active patients or patients with pre-existing LV dysfunction
 - LV dysfunction: Postoperative occurrence of PPM is associated with less regression of LV mass, thus associated with depressed LV function.
 - Bleeding: persistent von Willebrand abnormalities, due to high transvalvular gradient, leads to hemolysis.
 - Reduced functional capacity: These patients have a relatively stenotic prosthesis with a pressure gradient across the prosthesis at rest and much more so with exercise.
 - They often do well in the intermediate term but have an impaired long-term survival and prognosis.
- **Prevention:** PPM may be prevented by avoiding valves ≤ 21 mm in the aortic position, and ≤ 27 mm in the mitral position, if possible, taking into account the patient's body size ⁽¹⁾.
- **Management:** Patients with evidence of PPM, especially severe PPM, should receive close follow-up. Valve reintervention may be considered if:
 - PPM is severe or associated with moderate or severe valve stenosis.
 - Mean transprosthetic gradient is high (30-35 mmHg).
 - If patient develops heart failure symptoms or LV systolic dysfunction.

N.B: mortality after cardiac surgeries:

- **CABG:** ~1–5% - Redo CABG: ~10%
- **MVR:** ~6% - MVR in patients > 70 years: 14% - MVR + CABG: 11% ⁽²⁾ - MV repair: ~1–3%
- **AVR:** ~3–4% (*up to 8% in patients with low EF*) - AVR+CABG: 6% - AVR in octogenarians: ~6–9%

(1) Charts correlating the in-vitro prosthetic diameter of each brand with the effective orifice area are available. For example, a 23 mm bioprosthesis in the aortic position has an EOA of $1.4 \pm 0.3 \text{ cm}^2$; for a patient with a BSA of 2 m^2 , the indexed EOA is $0.7 \text{ cm}^2/\text{m}^2$, consistent with PPM. A 25 mm bioprosthesis (EOA 1.7 cm^2).

(2) Mainly due to the higher baseline comorbidity of these patients; the risk is related to CAD rather than CABG itself and is potentially higher if CAD is left untreated.

- AVR + aortic aneurysm repair: 9%
- **Multiple valve replacement:** 9%
- **Redo valve replacement:** 5–15%.

Differential diagnosis of a high transvalvular prosthetic gradient:

A high gradient, up to a certain degree, may be seen with a normally functioning prosthetic valve **or** may be due to four states:

1. Prosthetic obstruction (thrombus, pannus, degenerative bioprosthesis).
2. Patient/Prosthesis Mismatch.
3. Pressure recovery in the case of a bileaflet valve: The smaller central orifice of the bileaflet valve gives rise to a high-velocity jet; this corresponds to a localized pressure drop that is largely recovered once the central flow joins flow originating from the two lateral orifices
4. High flow state, subvalvular obstruction, or significant regurgitation across the valve.

The following ideas help establish the diagnosis:

- A velocity of up to 3 m/s across the aortic prosthesis (mean gradient up to 20 mmHg) and 1.9 m/s across the mitral prosthesis (gradient up to 6 mmHg) is within the normal range unless the cardiac output is low, in which case a low dimensionless index (DI) will suggest valvular obstruction.
- A high DI ($VTI_{LVOT}/VTI_{Aortic} > 0.30$) with aortic prosthesis, **or** low DI ($VTI_{Mitral}/VTI_{LVOT} < 2.2$) with mitral prosthesis usually implies: a high flow state, an associated subvalvular obstruction, or prosthetic aortic regurgitation. The calculated EOA would be within normal range.
- A valve with a small reference EOA on the manufacturer's chart and a small indexed EOA for the particular patient is diagnostic of *PPM*, which is by far the most common cause of a high transprosthetic gradient. In this case, the small calculated EOA matches the manufacturer's EOA.

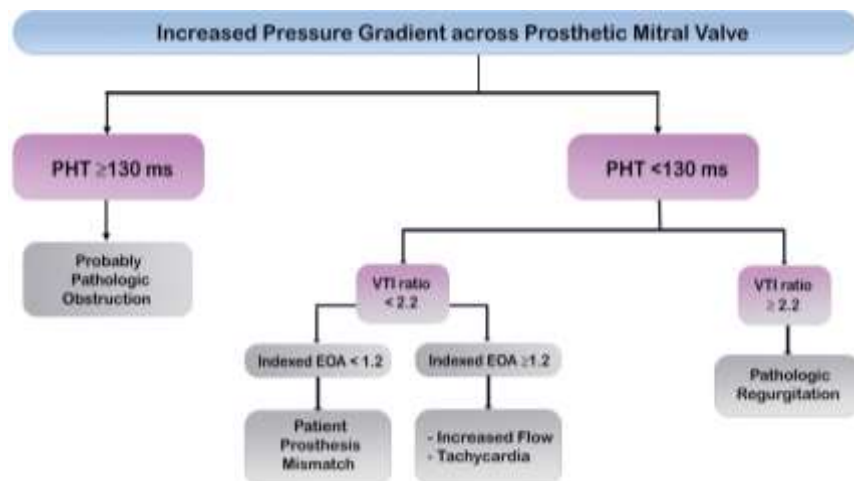


Figure 11-20: Echocardiographic approach to determine the diagnosis of a high transvalvular prosthetic gradient across the prosthetic mitral valve.

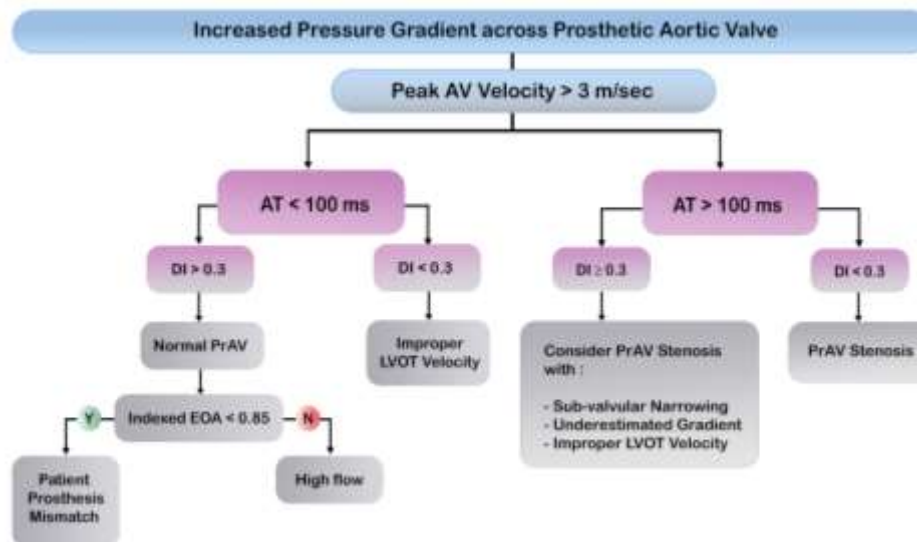


Figure 11-21: Echocardiographic approach to determine the diagnosis of a high transvalvular prosthetic gradient across the prosthetic aortic valve.

Management of prosthetic valve dysfunction:

| Table 11-23: ESC Recommendations on management of prosthetic valve dysfunction: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Mechanical prosthetic thrombosis: | | |
| Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity. | I | B |
| Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH or streptokinase 1 500 000 U in 60 min without UFH) should be considered when surgery is not available <u>or</u> is very high risk, <u>or</u> for thrombosis of right-sided prostheses. | IIa | B |
| Surgery should be considered for large (> 10 mm) non-obstructive prosthetic thrombus complicated by embolism. | IIa | C |
| Bioprosthetic thrombosis: | | |
| Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering re-intervention. | I | C |
| Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution. | IIa | B |
| Haemolysis and paravalvular leak: | | |
| Reoperation is recommended if a paravalvular leak is related to endocarditis <u>or</u> causes haemolysis requiring repeated blood transfusions <u>or</u> leading to severe heart failure symptoms. | I | C |
| Transcatheter closure should be considered for suitable paravalvular leaks with clinically significant regurgitation and/or haemolysis in patients at high or prohibitive surgical risk. | IIa | B |
| Decision on transcatheter or surgical closure of clinically significant paravalvular leaks should be considered based on patient risk status, leak morphology, and local expertise. | IIa | C |

| Bioprosthetic failure: | | |
|--|------------|----------|
| <i>Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.</i> | I | C |
| <i>Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction if reoperation is low risk.</i> | IIa | C |
| <i>Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomic considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable.</i> | IIa | B |
| <i>Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical re intervention.</i> | IIb | B |

Management during non-cardiac surgery

CV morbidity and mortality are increased in patients with VHD who undergo non-cardiac surgery.

Symptomatic severe aortic stenosis or mitral stenosis may require valve replacement or percutaneous intervention before non-cardiac surgery.

Preoperative evaluation:

Patient and surgical specific factors dictate the strategy.

Echocardiography should be performed in any patient with VHD requiring NCS.

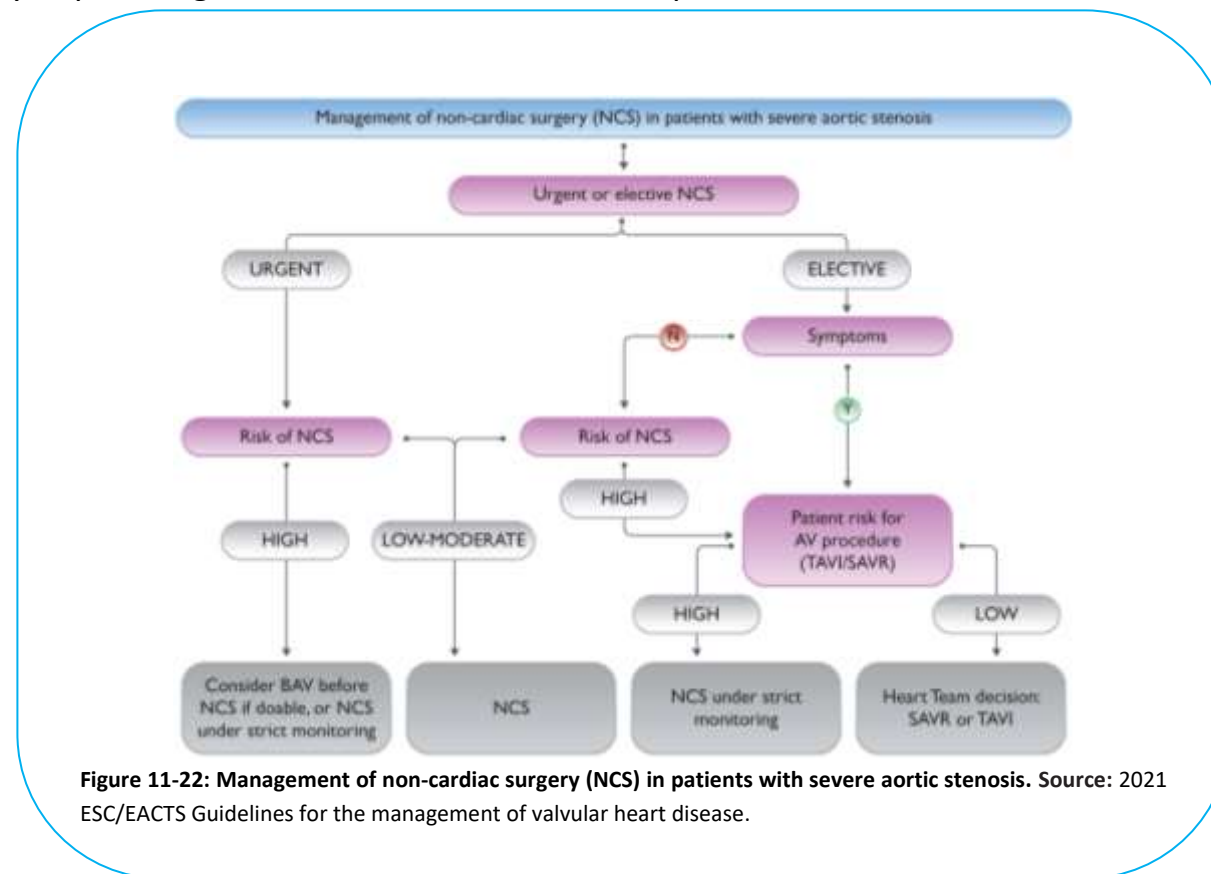
Determination of functional capacity is a pivotal step in preoperative risk assessment, measured either by ability to perform activities in daily life or by exercise test.

The decision for management should be taken after multidisciplinary discussion involving cardiologists, surgeons, and cardiac anaesthesiologists, as well as the team who will be in charge of NCS.

▪ **Aortic stenosis:**

- In patients with severe AS, urgent non-cardiac surgery should be performed under careful haemodynamic monitoring.

- The management related to elective non-cardiac surgery (NCS) depends on the presence of symptoms and the type of surgery.
 - In symptomatic patients, aortic valve replacement should be considered before non-cardiac surgery. In patients at increased surgical risk, TAVI is a therapeutic option.
 - In asymptomatic patients, elective non-cardiac surgery can be performed safely, albeit with a risk of worsening heart failure.
 - If noncardiac surgery implies large volume shifts, aortic valve replacement should be considered first.



▪ **Mitral stenosis:**

- Non-cardiac surgery can be performed safely in patients with non-significant mitral stenosis ($MVA > 1.5 \text{ cm}^2$) **and** in asymptomatic patients with significant MS and $sPAP < 50 \text{ mmHg}$.
- In symptomatic patients **or** in patients with systolic pulmonary artery pressure $> 50 \text{ mmHg}$, correction of mitral stenosis, by PMC if possible, should be attempted before non-cardiac surgery if it is high risk.

▪ **Aortic and mitral regurgitation:**

- Non-cardiac surgery can be performed safely in asymptomatic patients with severe MR or AR and preserved LV function.
- The presence of symptoms **or** LV dysfunction should lead to consideration of valvular surgery, but this is seldom needed before non-cardiac surgery.
- If LV dysfunction is severe ($LVEF < 30\%$), non-cardiac surgery should be performed only if strictly necessary, after optimization of medical therapy for HF.

Management during pregnancy

During pregnancy, the hypercoagulable state increases the risk of mechanical valve thromboembolic complications even with appropriate anticoagulation. The maternal mortality is 1-4% in patients with mechanical valves. Moreover, warfarin has fetal risks between 6 and 12 weeks and has to be replaced with UFH or LMWH during this period. LMWH and UFH are not as effective as warfarin in pregnancy; most valvular thromboembolic events in pregnancy occur while the mother is receiving heparin (9% if heparin is used between 6 and 12 weeks versus 4% with warfarin).

▪ **Management before pregnancy:**

- Pregnancy should be discouraged, and intervention is recommended before pregnancy in the following:
 - Patients with mitral stenosis and $MVA < 1.5 \text{ cm}^2$ (especially if $< 1.0 \text{ cm}^2$).
 - All symptomatic patients with severe AS **or** asymptomatic patients with impaired LV function ($LVEF < 50\%$) or an abnormal exercise test.

- Women with Marfan syndrome and an aortic diameter > 45 mm because of the high risk of aortic dissection. Although an aortic diameter < 40 mm is rarely associated with aortic dissection, a completely safe diameter does not exist. With an aortic diameter between 40 and 45 mm, previous aortic growth and family history are important for advising pregnancy with or without aortic repair.
- Bicuspid valves in the setting of aortic diameters > 50 mm (> 27 mm² BSA).
- Aortic diameter > 25 mm/m² BSA in Turner syndrome.
- All patients with vascular Ehlers-Danlos syndrome are also contraindications for pregnancy.
- In women considering pregnancy and requiring heart valve replacement, it is recommended to choose the prosthesis in consultation with a pregnancy Heart Team.
- Pregnancy in women with a mechanical valve, especially in the mitral position, is associated with a high risk of maternal and foetal complications, which should be discussed with the patient and family.
- **Management during pregnancy:**
 - **Patients with native valve disease:**
 - Significant mitral stenosis with MVA < 1.5 cm² in pregnant women is usually poorly tolerated. PMC should be considered in severely symptomatic patients (NYHA class III-IV) and/or those with SPAP > 50 mmHg despite optimal therapy. PMC should preferably be performed after the 20th week of pregnancy in experienced centres.
 - In patients with severe AS who are severely symptomatic despite medical therapy, Balloon aortic valvuloplasty can be undertaken by an experienced operator. Surgery under cardiopulmonary bypass is associated with a foetal mortality rate of 15-56% and should be restricted to the rare conditions that threaten the mother's life if transcatheter intervention is not possible or has failed.
 - **Mode of delivery:** Caesarean section is recommended for patients with severe mitral or aortic stenosis, ascending aortic diameter > 45 mm, severe pulmonary hypertension, or if delivery starts while treated with a VKA or < 2 weeks after discontinuation of a VKA.
 - **Mechanical prosthesis:**

Therapeutic anticoagulation during pregnancy is of utmost importance to avoid complications in these patients, keeping in mind that no anticoagulation regimen is ideal, and management will require a careful balance between maternal and foetal risks.

- In patients requiring < 5 mg/day warfarin, oral anticoagulants throughout pregnancy and a change to UFH before delivery is favoured.
- In patients requiring higher doses, switching to LMWH during the first trimester with strict anti-Xa monitoring (therapeutic range 0.8-1.2 IU/mL for aortic valve prosthesis; and 1.0-1.2 IU/mL for mitral and right sided valve prosthesis) and the use of oral anticoagulants afterwards is favoured with a change to UFH before delivery.

| Table 11-24: Clinical trials of Valvular Heart diseases: | |
|--|---|
| Trial (date) | Summary |
| MIDA (2013) | <p>Aim: To compare early surgery with medical management in patients with flail MR but without a class I indication for surgical correction.</p> <p>Study: Among registry of 1021 patients with MR due to flail mitral leaflets, performance of early mitral surgery compared with initial medical management was associated with greater long-term survival and a lower risk of heart failure, with no difference in new-onset AF.</p> |
| RECOVERY (2019) | <p>Aim: To assess the safety and benefit of surgery vs. watchful waiting among patients with asymptomatic very severe AS.</p> <p>Study: 145 eligible patients with very severe asymptomatic AS were randomized to either early surgical aortic valve replacement (AVR) or watchful waiting. The incidence of the composite of operative mortality or CV mortality during the follow-up period was significantly lower among those who underwent early AVR surgery than among those who received conservative care.</p> |
| CTCR-MVS (2021) | <p>Aim: To assess the safety and efficacy of concomitant tricuspid repair in patients with less than severe TR who were undergoing MV surgery.</p> <p>Study: 401 patients were randomized to either concomitant mitral valve surgery + tricuspid valve repair or mitral valve surgery alone. Tricuspid valve repair was performed using annuloplasty band. Concomitant tricuspid valve repair at the time of mitral valve surgery among patients with < severe TR at baseline results in improved outcomes at 2 years, primarily in reducing the progression to worse/severe TR. Endpoints such as mortality, readmission were similar, while permanent pacemaker implantation was higher with concomitant tricuspid valve repair.</p> |
| RE-ALIGN (2013) | <p>Aim: To assess if Dabigatran prevent thromboembolic complications in mechanical heart valve patients.</p> <p>Study: 252 patients who had undergone AV or MV-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier were randomly assigned to receive either dabigatran or warfarin. Doses were adjusted to obtain a trough plasma level of at least 50 ng/mL. The warfarin dose was adjusted</p> |

| | |
|-------------------------|---|
| | <i>to obtain an INR of 2-3 or 2.5-3.5 on the basis of thromboembolic risk. The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.</i> |
| MitraClip: | |
| COAPT (2018) | <p>Aim: <i>To assess the safety and efficacy of transcatheter mitral leaflet approximation using MitraClip in symptomatic HF patients with secondary MR.</i></p> <p>Study: <i>614 patients with heart failure and moderate-to-severe or severe secondary MR who remained symptomatic despite the use of maximal doses of GDMT were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all cause mortality and HF hospitalizations within 24 months of follow-up. Transcatheter mitral-valve repair resulted in a lower rate of HF hospitalization and lower all-cause mortality within 24 months of follow-up than medical therapy alone.</i></p> |
| MITRA-FR (2018) | <p>Aim: <i>To evaluate the clinical efficacy and safety of percutaneous mitral-valve repair in patients with HF and severe secondary MR.</i></p> <p>Study: <i>304 patients who had severe secondary MR (defined as an EROA > 20 mm² or regurgitant volume of > 30 ml/beat), LVEF between 15 and 40%, and symptomatic heart failure were randomly assigned to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group) or to receive medical therapy alone (control group). Among patients with severe secondary MR, the rate of death or unplanned HF hospitalization at 1 year did not differ significantly between both the intervention and control groups.</i></p> |
| TAVI: | |
| TAVI vs SAVR: | |
| PARTNER B (2010) | <p>Aim: <i>To compare outcomes between TAVR in patients who were not considered to be suitable candidates for surgery</i></p> <p>Study: <i>358 patients with severe AS who were not considered to be suitable candidates for surgery were randomly assigned to standard therapy (including balloon aortic valvuloplasty) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve. The primary end point was the rate of death from any cause. TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of</i></p> |

| | |
|-------------------------|--|
| | <i>death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events.</i> |
| PARTNER A (2011) | <p>Aim: <i>To compare outcomes between TAVR (either transfemoral or transapical) versus SAVR in patients who were high risk.</i></p> <p>Study: <i>699 high-risk patients with severe AS were randomly assigned to undergo either transcatheter aortic-valve replacement with a balloon-expandable bovine pericardial valve or surgical replacement. The primary end point was death from any cause at 1 year. TAVR and SAVR were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks.</i></p> |
| PARTNER 2 (2016) | <p>Aim: <i>To assess the safety and efficacy of balloon-expandable TAVR compared with SAVR in intermediate-risk patients.</i></p> <p>Study: <i>2032 intermediate-risk patients with severe AS were randomly assigned to undergo either TAVR or surgical replacement. The primary end point was death from any cause or disabling stroke at 2 years. The primary hypothesis was that TAVR would not be inferior to surgical replacement. TAVR was similar to SAVR with respect to the primary end point of death or disabling stroke in intermediate-risk patients.</i></p> |
| SURTAVI (2017) | <p>Aim: <i>To assess the safety and efficacy of TAVR with the self-expanding CoreValve compared with SAVR in intermediate-risk patients.</i></p> <p>Study: <i>1746 patients with severe AS were randomly assigned to undergo either TAVR or SAVR. TAVR was performed with the self-expanding CoreValve Classic (84%) in the majority of cases. Stratification was further performed based on significant CAD to either PCI (in the TAVR arm) or concomitant CABG (in the AVR arm). The primary end point was a composite of death from any cause or disabling stroke at 24 months. TAVR was a noninferior alternative to surgery in patients with severe AS at intermediate surgical risk, with a different pattern of periprocedural adverse events.</i></p> |
| PARTNER 3 (2019) | <p>Aim: <i>To evaluate TAVR compared with SAVR among low-risk patients with symptomatic severe aortic stenosis.</i></p> <p>Study: <i>1000 patients with severe AS and low surgical risk were randomly assigned to undergo either TAVR with transfemoral placement of a balloon-expandable valve or surgery. The primary end point was a composite of death, stroke, or rehospitalization at 1 year. The rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than with surgery.</i></p> |

| | |
|-----------------------------------|---|
| Evolut Low Risk (2019) | <p>Aim: To assess the safety and efficacy of TAVR with the self-expanding CoreValve compared with SAVR in low-risk patients.</p> <p>Study: 1468 patients who had severe aortic stenosis and were at low surgical risk were randomly assigned to an attempted TAVR or surgical procedure. TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the composite endpoint of death or disabling stroke at 24 months.</p> |
| Antithrombotic after TAVI: | |
| GALILEO (2019) | <p>Aim: To evaluate a rivaroxaban-based strategy compared with antiplatelet-based strategy among patients who underwent TAVR.</p> <p>Study: 1644 patients without an established indication for OAC after successful TAVR were randomly assigned to receive rivaroxaban at a dose of 10 mg daily (with aspirin at a dose of 75 to 100 mg daily for the first 3 months) (rivaroxaban group) <u>or</u> aspirin at a dose of 75 to 100 mg daily (with clopidogrel at a dose of 75 mg daily for the first 3 months) (antiplatelet group). Treatment strategy including rivaroxaban (10 mg daily) was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy.</p> |
| ATLANTIS (2022) | <p>Aim: To assess the efficacy and safety of apixaban 5 mg BID compared with standard of care (APT or VKA) among patients undergoing TAVR.</p> <p>Study: After successful TAVI, 1500 patients were randomized to receive apixaban 5 mg (2.5 mg if impaired renal function or concomitant antiplatelet therapy) twice daily, or standard of care (VKA or antiplatelet therapy if there was an indication for anticoagulation or not, respectively). Apixaban was not superior to the standard of care.</p> |
| POPular TAVI (2020) | <p>Aim: To evaluate OAC alone compared with OAC plus clopidogrel among patients who underwent TAVR and had a long-term indication for OAC.</p> <p>Study: 313 patients who were receiving oral anticoagulation were assigned before TAVI to receive clopidogrel for 3 months or not to receive clopidogrel. The two primary outcomes were all bleeding and non–procedure-related bleeding over a period of 12 months. The incidence of serious bleeding over 1 month or 1 year was lower with OAC alone than with OAC plus clopidogrel.</p> |

| | |
|--|---|
| POPular TAVI EU (2020) | <p>Aim: <i>To compare aspirin alone with aspirin + clopidogrel among patients who underwent TAVR and did not have a long-term indication for OAC.</i></p> <p>Study: <i>665 patients who were undergoing TAVI and did not have an indication for long-term anticoagulation were randomly assigned to receive aspirin alone or aspirin plus clopidogrel for 3 months. The two primary outcomes were all bleeding (including minor, major, and life-threatening or disabling bleeding) and non–procedure-related bleeding over a period of 12 months. The incidence of bleeding and the composite of bleeding or thromboembolic events at 1 year were significantly less frequent with aspirin than with aspirin plus clopidogrel administered for 3 months.</i></p> |
| Transcatheter TV repair: | |
| TRILUMIN ATE Pivotal (2023) | <p>Aim: <i>To evaluate percutaneous tricuspid valve transcatheter edge-to-edge repair (TEER) compared with medical therapy among patients with symptomatic severe TR.</i></p> <p>Study: <i>350 patients with symptomatic severe tricuspid regurgitation were assigned to receive either TEER or medical therapy (control). The primary end point was a hierarchical composite that included death from any cause or tricuspid-valve surgery; hospitalization for heart failure; and an improvement in quality of life (improvement defined as an increase of at least 15 points in the KCCQ score) at the 1-year follow-up. Tricuspid TEER was safe for patients with severe TR, reduced the severity of TR, and was associated with an improvement in quality of life.</i></p> |

References and suggested readings:

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- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
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Chapter 12:

Infective Endocarditis

Prevention:

- **Populations at risk of IE:**

- **High-risk populations:** In this category, antibiotic prophylaxis is recommended or should be considered:

1. Patients with previous IE.
2. Patients with surgically/transcatheter implanted prosthetic valves, and with any material used for cardiac valve repair: this category includes ASD, VSD, and LAA closure devices, vascular grafts, vena cava filters, and central venous system ventriculo-atrial shunts within the first 6 months after implantation.
3. Patients with ventricular assist devices as destination therapy.
4. Patients with untreated cyanotic congenital heart disease (not including isolated congenital valve abnormalities), and patients treated with surgical or transcatheter palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.

- **Intermediate risk population:** In this category, antibiotic prophylaxis is not routinely recommended and may be considered on an individual basis. This category includes: **(i)** rheumatic heart disease (RHD); **(ii)** non-rheumatic degenerative valve disease; **(iii)** congenital valve abnormalities including bicuspid aortic valve; **(iv)** cardiac implanted electronic devices (CIEDs); and **(v)** hypertrophic cardiomyopathy.

- **Situations and procedures at risk:**

- **Dental procedures:** Antibiotic prophylaxis is recommended in patients at high risk of IE undergoing at-risk dental procedures. At-risk dental procedures include dental extractions, oral surgery procedures (including periodontal surgery, implant surgery, and oral biopsies), and dental procedures involving manipulation of the gingival or periapical region of the teeth (including scaling and root canal procedures). There is no evidence to contraindicate implants in all patients at risk.

- **Non-dental procedures:** there is no convincing evidence on the relationship between bacteraemia resulting from a non-dental procedure and risk of subsequent IE.
- **Cardiac or vascular interventions:**
 - In all patients undergoing implantation of a prosthetic valve, any type of prosthetic graft/occluder device or CIED, peri-operative antibiotic prophylaxis is recommended.
 - Pre-operative screening of nasal carriage for *S. aureus* is recommended before elective cardiac surgery or transcatheter valve implantation to treat carriers using local mupirocin and chlorhexidine.
 - It is strongly recommended that potential sources of dental sepsis should be eliminated at least 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material unless the latter procedure is urgent.

| Table 12-1: ESC Recommendations for prophylaxis of IE: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| IE prevention in high-risk procedures: | | |
| <i>Antibiotic prophylaxis is recommended in dental extractions, oral surgery procedures, and procedures requiring manipulation of the gingival or periapical region of the teeth.</i> | I | B |
| <i>Systemic antibiotic prophylaxis may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems.</i> | IIb | C |
| IE prevention in patients at increased risk for IE undergoing oro-dental procedures: | | |
| <i>General prevention measures are recommended in individuals at high and intermediate risk for IE.</i> | I | C |

| | | |
|---|-----|---|
| Antibiotic prophylaxis is recommended in patients with: | | |
| ○ Previous IE. | I | B |
| ○ Surgically implanted prosthetic valves and with any material used for surgical valve repair. | I | C |
| ○ Transcatheter implanted aortic and pulmonary valvular prostheses. | I | C |
| ○ Untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure. | I | C |
| ○ Ventricular assist devices. | I | C |
| Antibiotic prophylaxis should be considered in patients with transcatheter mitral and tricuspid valve repair. | IIa | C |
| Antibiotic prophylaxis may be considered in recipients of heart transplant. | IIb | C |
| Antibiotic prophylaxis is not recommended in other patients at low risk for IE. | III | C |
| IE prevention in cardiac procedures: | | |
| Pre-operative screening for nasal carriage of <i>S. aureus</i> is recommended before elective cardiac surgery or transcatheter valve implantation to treat carriers. | I | A |
| Peri-operative antibiotic prophylaxis is recommended: | | |
| ○ before placement of a CIED. | I | A |
| ○ in patients undergoing surgical or transcatheter implantation of a prosthetic valve, intravascular prosthetic, or other foreign material. | I | B |
| Antibiotic prophylaxis covering for common skin flora including <i>Enterococcus</i> spp. and <i>S. aureus</i> should be considered before TAVI and other transcatheter valvular procedures. | IIa | C |
| Optimal pre-procedural aseptic measures of the site of implantation is recommended to prevent CIED infections. | I | B |

| | | |
|---|------------|----------|
| <i>Surgical standard aseptic measures are recommended during the insertion and manipulation of catheters in the catheterization laboratory environment.</i> | I | C |
| <i>Elimination of potential sources of sepsis (including of dental origin) should be considered ≥ 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, except in urgent procedures.</i> | IIa | C |
| <i>Systematic skin or nasal decolonization without screening for <i>S. aureus</i> is not recommended.</i> | III | C |

| Table 12-2: Recommended prophylaxis for high-risk dental procedures in high-risk patients: | | | |
|---|---|---|---|
| Situation | Antibiotic | Single-dose 30-60 min before procedure | |
| | | Adults | Children |
| No allergy to penicillin | Amoxicillin or ampicillin | 2 g PO or i.v. | 50 mg/kg PO or i.v. |
| | Cefazolin or ceftriaxone | 1 g i.m. or i.v. | 50 mg/kg i.v. or i.m. |
| Allergy to penicillin | Cephalexin | 2 g PO | 50 mg/kg PO |
| | Azithromycin <u>or</u> clarithromycin | 500 mg PO | 15 mg/kg PO |
| | Doxycycline | 100 mg PO | < 45 kg, 2.2 mg/kg PO > 45 kg, 100 mg PO |
| | Cefazolin or ceftriaxone ⁽¹⁾ | 1 g i.m. or i.v. | 50 mg/kg i.v. or i.m. |

| Table 12-3: General prevention measures to be followed in patients at high-risk and intermediate-risk of IE: |
|--|
| These measures should be applied to the general population and particularly reinforced in high-risk patients: |
| <i>Patients should be encouraged to maintain twice daily tooth cleaning and to seek professional dental cleaning and follow-up at least twice yearly for high-risk patients and yearly for others.</i> |

(1) Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with penicillin.

| |
|--|
| <i>Strict cutaneous hygiene, including optimized treatment of chronic skin conditions.</i> |
| <i>Disinfection of wounds.</i> |
| <i>Curative antibiotics for any focus of bacterial infection.</i> |
| <i>No self-medication with antibiotics.</i> |
| <i>Strict infection control measures for any at-risk procedure.</i> |
| <i>Discouragement of piercing and tattooing.</i> |
| <i>Limitation of infusion catheters and invasive procedures when possible.</i> |
| <i>Strict adherence to care bundles for central and peripheral cannulae should be performed.</i> |

Diagnosis:

The diagnosis of IE is based on a clinical suspicion supported by consistent microbiological data and the documentation of IE-related cardiac lesions by imaging techniques.

▪ **Clinical Features:** In general, a diagnosis of IE should be considered in all patients with:

- Fever and positive blood cultures in the absence of an alternative focus of infection, especially in patients with one or more risk factors.
- Any patient presenting with fever and embolic phenomena (Up to 25% of patients have embolic complications at the time of diagnosis).

▪ **Imaging techniques:**

• **Echocardiography:**

- When IE is suspected, TTE and TOE are often both required. TTE had low sensitivity, but good specificity as compared with TOE.

- Vegetation characteristics and size ⁽¹⁾, perivalvular complications (abscess, pseudoaneurysm, new partial dehiscence of prosthetic valve), intracardiac fistula, and leaflet perforation are the main findings for the diagnosis and evaluation of local complications of IE.
- TOE is helpful in diagnosis of perivalvular complications, small vegetations, PVE, and vegetations associated with CIED.
Therefore, TOE is strongly recommended in: **(i)** patients with an inconclusive TTE, **(ii)** patients with a negative TTE and a high suspicion of IE, **(iii)** patients with a positive TTE in order to document local complications, **(iv)** prosthetic heart valve or an intracardiac device.
- TOE may miss vegetations in 5-10% of patients, particularly in the following cases: **(i)** very early stage, **(ii)** Very small vegetation < 3 mm, **(iii)** Pre-existing, severe valvular lesion (myxomatous mitral valve, calcified AS, prosthetic valve).
- Echocardiography (TTE and/or TOE) should be repeated 5-7 days after an initial normal or inconclusive echocardiography, if the suspicion of IE remains high, **and** in patients with diagnosed IE at high risk of complications (e.g., *S. aureus* bacteremia in a patient with prosthetic valve and negative initial TEE).
- **CT:** The indications for CT in patients with suspected or diagnosed IE include:
 - Diagnosis of IE cardiac complications: Cardiac CT is more accurate than TOE for diagnosing perivalvular and periprosthetic complications of IE (abscesses, pseudoaneurysms, and fistulae) and is recommended in both NVE and PVE if TOE is not conclusive or not feasible.
 - Detection of distant lesions and sources of bacteraemia: Whole-body and brain CT are useful for assessing IE systemic complications, including septic emboli and mycotic arterial aneurysms.
 - Pre-operative assessment of coronary artery disease before cardiac surgery in patients with IE.
 - Alternative diagnosis: In patients in whom IE is ruled out, an alternative diagnosis can be reached by whole-body CT. However, in these circumstances, an [18]FDG PET/CT is the preferred imaging technique.
- **MRI:** The roles of MRI in the diagnostic work-up of IE include:

(1) vegetation size is defined as the maximal length of the vegetation.

- Diagnosis of neurological IE-related complications. Patients with IE might present CNS lesions in up to 60–80% of cases, most of them corresponding to ischaemic lesions that are often small and asymptomatic. The systematic performance of brain MRI has shown to directly impact the diagnosis of IE, as it can add a minor diagnostic criterion in patients without neurological symptoms with non-definitive IE diagnosis.
- Diagnosis of spine lesions. MRI is the diagnostic modality of choice of spondylodiscitis and vertebral osteomyelitis. When MRI is performed too early, the rate of false-negative increases.
- **Nuclear imaging PET/CT and single PET/CT:** The roles of nuclear imaging in the work-up of IE include:
 - Diagnosis of IE and cardiac complications. [18F]FDG-PET/CT and WBC-SPECT/CT are recommended in suspected PVE in cases of inconclusive echocardiography.
 - Detection of distant lesions and sources of bacteraemia. Whole-body [18F]FDG-PET/CT imaging is particularly useful in patients with a suspicion or proven IE to identify distant lesions, septic emboli ⁽¹⁾, mycotic aneurysms, and the portal of entry of the infection.
 - Monitoring response to antimicrobial treatment with [18F] FDG-PET/CT in patients with established IE and indication for surgery but who cannot be operated on due to unacceptable high risk and remain with long-term suppressive antibiotic treatment.

Table 12-4: Anatomical definitions of IE lesions and complications

| Definition | |
|-------------------|---|
| Vegetation | <i>Infected mass attached to valve or other endocardial structure or on implanted intracardiac material.</i> |
| Abscess | <i>Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen.</i> |

(1) [18F] FDG-PET/CT is less suited to detect cerebral septic embolism and mycotic aneurysms of intracerebral arteries due to the high physiological uptake of [18F]FDG in the brain.

| | |
|---|---|
| | On Echo: Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance. |
| Pseudoaneurym | Perivalvular cavity communicating with the cardiovascular lumen. On Echo: Pulsatile perivalvular echo free space, with colour-Doppler detected. |
| Perforation | Interruption of endocardial tissue continuity (traversed by colour-Doppler on echo). |
| Fistula | Communication between two neighbouring cavities through a perforation (traversed by colour-Doppler on echo). |
| Valve aneurysm | Saccular bulging of valvular tissue. |
| Dehiscence of a prosthetic valve | Dehiscence of the prosthesis. On Echo: Paravalvular regurgitation with or without rocking motion of the prosthesis. |

| Table 12-5: ESC recommendations for role of echocardiography in IE: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Echocardiography: | | |
| A. Diagnosis: | | |
| TTE is recommended as the first-line imaging modality in suspected IE. | I | B |
| TOE is recommended in all patients with clinical suspicion of IE: | | |
| - and negative or non-diagnostic TTE. | I | B |
| - when a prosthetic heart valve or an intracardiac device is present. | I | B |
| | I | C |

| | | |
|---|-----|---|
| - even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings. | | |
| Repeating TTE and/or TOE within 5-7 days is recommended in case of initially negative examination or inconclusive examination when clinical suspicion of IE remains high. | I | C |
| Performing an echocardiography should be considered in <i>S. aureus</i> , <i>E. faecalis</i> , and some <i>Streptococcus spp. bacteraemia</i> . | IIa | B |
| B. Follow-up under medical therapy: | | |
| Repeating TTE and/or TOE is recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, HF, abscess, AV block). | I | B |
| Repeat TTE and/or TOE should be considered in uncomplicated IE to detect new silent complications. The timing of repeat TTE and/or TOE depends on the initial findings, type of microorganism, and initial response to therapy. | IIa | B |
| TOE is recommended when patient is stable before switching from intravenous to oral antibiotic therapy. | I | B |
| C. Intraoperative echocardiography: | | |
| Intraoperative echocardiography is recommended in all cases of IE requiring surgery. | I | B |
| D. Following completion of therapy: | | |
| TTE and/or TOE are recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function in patients with IE who did not undergo heart valve surgery. | I | C |
| CT, nuclear imaging, and MRI in IE: | | |
| Cardiac CTA is recommended in patients with possible NVE to detect valvular lesions and confirm the diagnosis of IE. | I | B |

| | | |
|---|------------|----------|
| <i>[18F]FDG-PET/CT(A) and cardiac CTA are recommended in possible PVE to detect valvular lesions and confirm the diagnosis of IE.</i> | I | B |
| <i>Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.</i> | I | B |
| <i>Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) are recommended in symptomatic patients (symptoms suggesting septic embolic complications) with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria</i> | I | B |
| <i>WBC SPECT/CT should be considered in patients with high clinical suspicion of PVE when echocardiography is negative or inconclusive and when PET/CT is unavailable.</i> | IIa | C |
| <i>[18F]FDG-PET/CT(A) may be considered in possible CIED-related IE to confirm the diagnosis of IE.</i> | IIb | B |
| <i>Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and MRI) in NVE and PVE may be considered for screening of peripheral lesions in asymptomatic patients.</i> | IIb | B |

▪ **Microbiological diagnosis:**

The most common organisms responsible for IE are: Staph. aureus (31%), followed by oral streptococci (17%), and coagulase-negative staphylococci (CoNS; 11%).

- **Blood culture-positive IE:** Positive blood cultures remain the cornerstone of IE diagnosis and provide live bacteria for both identification and susceptibility testing. At least three sets of blood cultures should be obtained at 30-min intervals prior to antibiotic therapy, each containing 10 mL of blood, and should be incubated in both aerobic and anaerobic atmospheres. Sampling should be obtained from a peripheral vein rather than from a central venous catheter (because of the risk of contamination and misleading interpretation), using a meticulous sterile technique.
Since there is a long delay between blood culture sampling and definitive identification of the organism and antibiotic susceptibility testing, many improvements have been proposed to speed up the process of detection (e.g., MALDI-TOF MS).

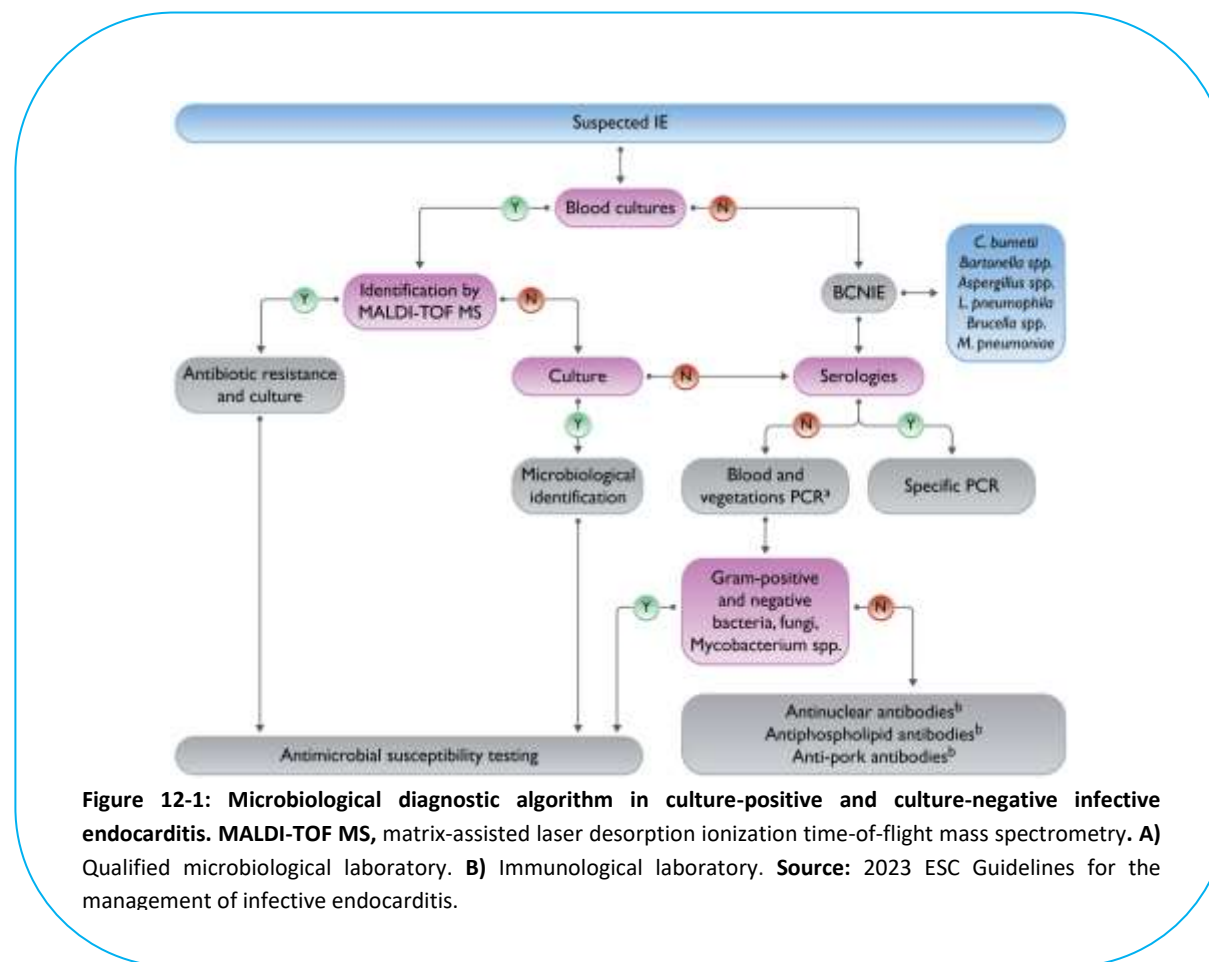
However, the gold standard for susceptibility testing is still the determination of the minimal inhibitory concentrations (MICs) to select appropriate antibiotic therapy.

- **Blood culture-negative IE (BCNIE):** BCNIE refers to IE in which no causative microorganism can be grown using the usual blood culture methods. BCNIE most commonly arises as a consequence of:
 - Previous antibiotic administration, underlying the importance of performing blood cultures prior to antibiotic therapy.
 - Fungi or fastidious bacteria, notably obligatory intracellular bacteria. Isolation of these microorganisms requires culturing on specialized media. Depending on local epidemiology, systematic serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumoniae*, *Brucella* spp., and *Legionella pneumophila* should be proposed, followed by specific PCR assays for *Tropheryma whipplei*, *Bartonella* spp., and fungi (*Candida* spp., *Aspergillus* spp.) from blood and the tissue.
 - Non-bacterial endocarditis should systematically be considered if all assays are negative and assays for antinuclear antibodies as well as antiphospholipid syndrome [anticardiolipin antibodies (IgG) and anti- β 2-glycoprotein 1 antibodies (IgG and IgM)] should be performed (although these antibodies may also be present in patients with proven IE).
- **Pathological examination** of resected tissue or embolic fragments is the gold standard for IE diagnosis.

Table 12-6: Investigation of rare causes of blood culture negative infective endocarditis:

| Pathogen | Diagnostic procedures |
|-----------------------------------|--|
| <i>Brucella</i> spp | <i>Serology, blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue.</i> |
| <i>Coxiella burnetii</i> | <i>Serology (IgG phase I > 1:800), tissue culture, immunohistology, and 16S rRNA sequencing of tissue.</i> |
| <i>Bartonella</i> spp. | <i>Serology (IgG phase I >1:800), blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue.</i> |
| <i>Tropheryma whipplei</i> | <i>Histology and 16S rRNA sequencing of tissue.</i> |
| <i>Mycoplasma</i> spp. | <i>Serology, tissue culture, immunohistology, and 16S rRNA sequencing of tissue.</i> |
| <i>Legionella</i> spp | <i>Serology, blood cultures, tissue culture, immunohistology, and 16S rRNA sequencing of tissue</i> |

| | |
|---------------------|---|
| Fungi | <i>Serology, blood cultures, 18S rRNA sequencing of tissue.</i> |
| Mycobacteria | <i>Specific blood cultures, 16S rRNA sequencing of tissue.</i> |



▪ Diagnostic criteria:

In 2000, the modified Duke criteria were recommended for diagnostic classification. However, the modified Duke criteria show a lower diagnostic accuracy for early diagnosis, especially in the case of PVE and CIED-related IE, for which echocardiography is normal or inconclusive in up to 30% of cases.

Table 12-7: Definitions of the 2023 ESC modified diagnostic criteria of IE:

Major criteria:

(I) Blood cultures positive for IE:

- A.** Typical microorganisms consistent with IE from two separate blood cultures: Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, *E. faecalis*
- B.** Microorganisms consistent with IE from continuously positive blood cultures:
 - ≥ 2 positive blood cultures of blood samples drawn > 12 h apart.
 - All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last samples drawn ≥ 1 h apart).
- C.** Single positive blood culture for *Coxiella burnetii* **or** phase I IgG antibody titre $>1:800$.

(II) Imaging positive for IE:

- Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:
- Echocardiography (TTE and TOE).
 - Cardiac CT.
 - [18F]-FDG-PET/CT(A).
 - WBC SPECT/CT.

Minor criteria:

- I.** Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE **or** PWIDs)
- II.** Fever defined as temperature $> 38^{\circ}\text{C}$.
- III.** Embolic vascular dissemination (including those asymptomatic detected by imaging only):

- Major systemic and pulmonary emboli/infarcts and abscesses.
- Haematogenous osteoarticular septic complications (Spondylodiscitis is the most frequent osteoarticular infective complication in patients with IE).
- Mycotic aneurysms
- Intracranial ischaemic/haemorrhagic lesions.
- Conjunctival haemorrhages.
- Janeway's lesions.

V. Immunological phenomena:

- Glomerulonephritis.
- Osler nodes and Roth spots.
- Rheumatoid factor.

V. Microbiological evidence:

- Positive blood culture but does not meet a major criterion as noted above.
- Serological evidence of active infection with organism consistent with IE.

IE Classification (at admission and during follow-up):

Definite:

- 2 major criteria.
- 1 major criterion and at least 3 minor criteria.
- 5 minor criteria.

Possible:

- 1 major criterion and 1 or 2 minor criteria.
- 4 minor criteria.

Rejected:

- *Does not meet criteria for definite or possible at admission with or without alternative diagnosis.*



Figure 12-2: Some peripheral signs of Infective endocarditis. (A) Janeway lesions are irregular, nontender hemorrhagic macules located on the palms, soles, thenar and hypothenar eminences of the hands, and plantar surfaces of the toes. They typically last for days to weeks. **(B) Osler's nodes** are split pea-sized, erythematous, tender nodules located principally on the pads of the fingers and toes. They occur in about 15% of patients with subacute bacterial endocarditis. The lesions are usually transient and clear in 1 to 2 days. **(C) Roth spots** are white-centered retinal hemorrhage. They have been detected in 80% of cases of subacute bacterial endocarditis. They are also seen in association with conditions including leukemia, anemia, hypertensive retinopathy, preeclampsia, diabetic retinopathy, and anoxia. **(D) Splinter hemorrhages** in endocarditis develop because of septic embolization from an original source of infection causing rupture of longitudinally oriented nail plate capillaries leading to extravasation and the historical hallmark of linear discoloration.

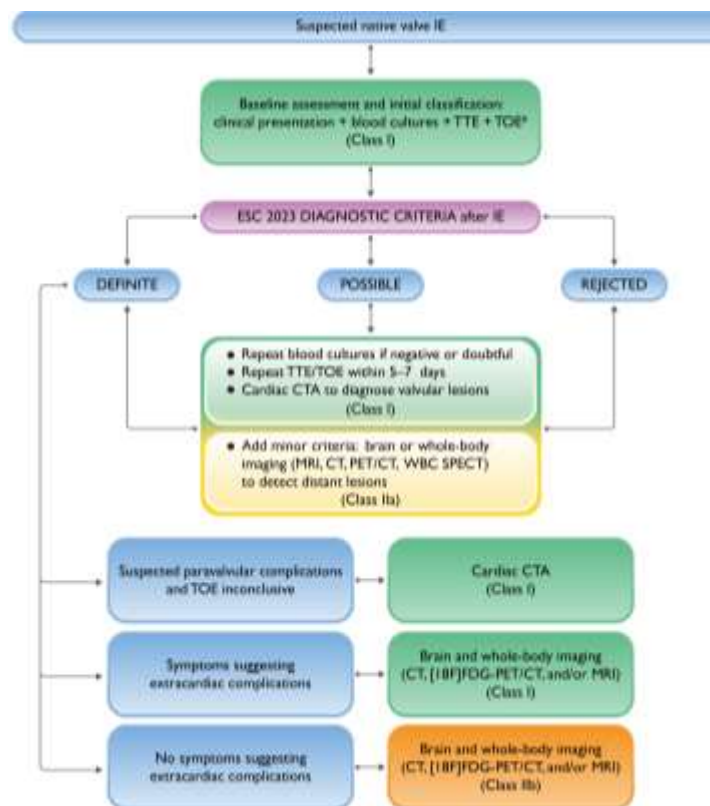


Figure 12-3: ESC 2023 algorithm for diagnosis of infective endocarditis. A) TOE for diagnosis and to detect perivalvular complications in all cases (unless right-sided NVE when TTE is good quality and conclusive). **(B)** In suspected prosthetic valve endocarditis, you can also consider [18F]FDG-PET/ CT to diagnose valvular lesion. **Source:** 2023 ESC Guidelines for the management of infective endocarditis.

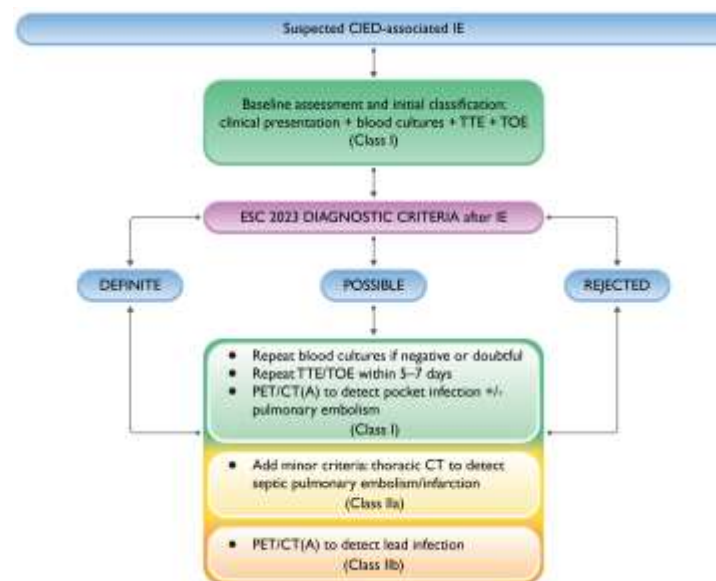


Figure 12-4: ESC 2023 algorithm for diagnosis of cardiac device-related infective endocarditis. Source: 2023 ESC Guidelines for the management of infective endocarditis.

Prognostic assessment at admission:

The in-hospital mortality rate of patients with IE varies from 15-30%. Rapid identification of patients at highest risk of death may offer the opportunity to change the course of the disease (i.e. emergency or urgent surgery) and improve prognosis.

Table 12-8: Predictors of poor outcome in patients with infective endocarditis:

Patient characteristics:

- *Older age*
- *Prosthetic valve IE*
- *Diabetes mellitus*
- *Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)*

Clinical complications of IE:

- *Heart failure*
- *Renal failure*
- *> Moderate area of ischaemic stroke*
- *Brain haemorrhage*
- *Septic shock*

Microorganism:

- *Staphylococcus aureus*
- *Fungi*
- *Non-HACEK Gram-negative bacilli*

Echocardiographic finding:

- *Periannular complications*
- *Severe left-sided valve regurgitation*
- *Low LVEF*
- *Pulmonary hypertension*
- *Large vegetations*
- *Severe prosthetic valve dysfunction*
- *Premature mitral valve closure and other signs of elevated diastolic pressures.*

Antimicrobial therapy:

- Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30-min. intervals before initiation of antibiotics.
- Successful treatment of IE relies on microbial eradication by antimicrobial drugs and surgical eradication of the infected tissues -in about 50% of patients-.
- One major hindrance to drug-induced killing is bacterial antibiotic tolerance. Tolerant microbes are not resistant (i.e., they are still susceptible to growth inhibition by the drug), but escape drug-induced killing and may resume growth after treatment discontinuation.
- Bactericidal drug combinations are preferred to monotherapy against tolerant organisms (e.g., the combination of ampicillin and ceftriaxone in IE caused by *E. faecalis*).
- **Empirical antimicrobial therapy:** The initial choice of empirical treatment depends on:
 - Previous antibiotic therapy.
 - IE in a native valve or a prosthesis (and if so, when surgery was performed [early vs. late PVE]).
 - The place of the infection (community, nosocomial, or non-nosocomial healthcare-associated IE).
 - Local epidemiology, especially for antibiotic resistance and culture-negative pathogens.
- Once the pathogen is identified (usually within 24 h), the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern. It should be emphasized that the empirical treatment should be changed to targeted therapy once the organism is identified within 24–48 h.
- **Duration of antimicrobial therapy:**
 - Drug treatment of PVE should last longer (≥ 6 weeks) than that of NVE (2-6 weeks).
 - In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy (negative blood culture in the case of initial positive blood culture), not on the day of surgery. A new full course of treatment should only start if valve cultures are positive.

- **Different strategies between NVE and PVE:**

- In NVE needing valve replacement by a prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE.
- NVE and late PVE regimens should cover staphylococci, streptococci, and enterococci.
- Coagulase negative staph. should be empirically covered in PVE but not in NVE.
- Early PVE or healthcare-associated IE regimens should cover methicillin-resistant staphylococci, enterococci and, ideally, non-HACEK Gram-negative pathogens.
- In staphylococcal PVE, the regimen should include rifampin whenever the strain is susceptible.

- **Notes regarding specific antibiotics:**

- Aminoglycosides synergize with cell wall inhibitors (i.e., beta-lactams and glycopeptides) for bactericidal activity and are useful for shortening the duration of therapy (e.g., oral streptococci) and eradicating problematic organisms. Aminoglycosides are not recommended in staphylococcal NVE because their clinical benefits have not been demonstrated. When they are indicated in other conditions (e.g. resistant oral streptococci), aminoglycosides should be given for no longer than 2 weeks to reduce nephrotoxicity.
- Rifampin should be used only in foreign body infections such as PVE after 3–5 days of effective antibiotic therapy, once the bacteraemia has been cleared. The rationale supporting this recommendation is based on the likely antagonistic effect of the antibiotic combinations with rifampin against planktonic/replicating bacteria, and the synergy seen against dormant bacteria within the biofilms and prevention of rifampin-resistant variants.
- Daptomycin at high doses (10 mg/kg once daily) has been recommended for treating staphylococcal and enterococcal endocarditis. To increase activity and avoid the development of resistance, it must be combined with beta-lactams or fosfomycin for NVE, and with gentamicin and rifampin for PVE.
- Fungi are most frequently observed in PVE and in IE affecting PWID or immunocompromised patients. Candida and Aspergillus spp. predominate, the latter resulting in BCNIE. Mortality is very high (> 50%), and treatment necessitates combined antifungal administration and with a low threshold for surgery. Antifungal therapy for Candida IE includes an echinocandin at high doses

or liposomal amphotericin B (or other lipid formulations) with or without flucytosine. For *Aspergillus* IE, voriconazole is the drug of choice. Suppressive longterm treatment with oral azoles (fluconazole and voriconazole) is recommended, sometimes lifelong.

| Table 12-9: ESC recommendations for antibiotic treatment of infective endocarditis: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Initial empirical antibiotic regimens for IE (before pathogen identification): | | |
| <i>In patients with community-acquired NVE or late PVE (≥ 12 months post-surgery), ampicillin in combination with ceftriaxone <u>or</u> with (flu)cloxacillin and gentamicin should be considered.</i> | IIa | C |
| <i>In patients with community-acquired NVE or late PVE (≥ 12 months post-surgery) who are allergic to penicillin, cefazolin or vancomycin combined with gentamicin may be considered.</i> | IIb | C |
| <i>In patients with early PVE (< 12 months post-surgery) or nosocomial and non-nosocomial healthcare-associated IE, vancomycin or daptomycin combined with gentamicin and rifampin may be considered.</i> | IIb | C |
| IE due to oral streptococci and <i>Strept. gallolyticus</i> group: | | |
| <i>Penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE).</i> | I | B |
| <i>In patients with IE due to oral streptococci and <i>S. gallolyticus</i>, who are allergic to beta-lactams: vancomycin for 4 weeks (in NVE) or for 6 weeks (in PVE) is recommended.</i> | I | C |
| <i>In patients with non-complicated NVE or PVE due to oral streptococci and <i>S. gallolyticus</i>: 2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended.</i> | I | B |
| <i>Staphylococcus</i> spp.: | | |
| <i>In patients with IE due to methicillin-susceptible staphylococci:</i> ○ <i>In NVE, (flu)cloxacillin or cefazolin is recommended for 4-6 weeks.</i> | I | B |

| | | |
|--|-----|---|
| ○ In PVE, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended. | | |
| In patients with IE due to methicillin-susceptible staphylococci who are allergic to penicillin: | | |
| ○ In NVE, cefazolin for 4-6 weeks is recommended. | I | B |
| ○ In NVE, daptomycin combined with ceftaroline or fosfomycin may be considered. | IIb | C |
| ○ In PVE, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended. | I | B |
| ○ In PVE, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered. | IIb | C |
| In patients with IE due to methicillin-resistant staphylococci (MRSA) ⁽¹⁾ : | | |
| ○ In NVE, vancomycin is recommended for 4-6 weeks. | I | B |
| ○ In NVE, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered. | IIb | C |
| ○ In PVE, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended. | I | B |
| Enterococcus spp.: | | |
| In patients with NVE due to non-HLAR Enterococcus spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended. | I | B |
| In patients with PVE and patients with complicated NVE or > 3 months of symptoms due to non-HLAR Enterococcus spp., the combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin for 2 weeks is recommended. | I | B |

(1) MRSA produces low-affinity penicillin-binding proteins, which confer cross-resistance to most beta-lactams. MRSA is usually resistant to multiple antibiotics, leaving vancomycin, daptomycin, ceftaroline, and dalbavancin to treat severe infections.

| | | |
|---|----------|----------|
| <i>In patients with NVE or PVE due to HLAR Enterococcus spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended.</i> | I | B |
| <i>In patients with IE due to beta-lactam resistant Enterococcus spp. (E. faecium), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended.</i> | I | C |
| <i>In patients with IE due to vancomycin-resistant Enterococcus spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended.</i> | I | C |

| Table 12-10: Recommended antibiotics dosage and route for management of IE: | | |
|--|---|---|
| Antibiotic | Adult antibiotic dosage and route | Pediatric antibiotic dosage and route |
| Penicillin G | 12–18 million U/day i.v. either in 4–6 doses or continuously | 200 000 U/kg/day i.v. in 4–6 divided doses |
| (Flu)cloxacillin | 12 g/day i.v. in 4–6 doses | 200–300 mg/kg/day i.v. in 4–6 equally divided doses |
| Ampicillin | 12 g/day i.v. in 4–6 doses | 300 mg/kg/day i.v. in 4–6 equally divided doses |
| Amoxicillin | 100–200 mg/kg/day i.v. in 4–6 doses | |
| Cefazolin | 6 g/day i.v. in 3 doses | |
| Ceftaroline ⁽¹⁾ | 1800 mg/day i.v. in 3 doses | |
| Ceftriaxone | 2 g/day i.v. in 1 dose | 100 mg/kg/day i.v. in 1 dose |

(1) High doses of ceftaroline may be associated with risk of leucopaenia after 2 weeks. Ceftaroline can replace cloxacillin only in patients with non–immediate-type hypersensitivity reactions to penicillin.

| | | |
|--------------------------|--|--|
| Vancomycin (1) | 30 mg/kg/day i.v. in 2 doses | |
| Gentamicin (2) | 3 mg/kg/day i.v. or i.m. in 1 dose | |
| Rifampin | 900 mg/day i.v. or orally in 3 equally divided doses | 20 mg/kg/day i.v. or orally in 3 equally divided doses |
| Daptomycin | 10 mg/kg/day i.v. in 1 dose | |
| Fosfomycin (3) | 8–12 g/day i.v. in 4 doses | |
| Ertapenem (4) | 2 g/day i.v. or i.m. in 1 dose | 1 g/day i.v. or i.m. in 1 dose [if < 12 years: 15 mg/kg/dose (max. 500 mg) B.I.D] |

▪ **Blood culture-negative IE:**

| Table 12-11: Antibiotic treatment of blood culture-negative infective endocarditis: | | |
|--|--|--|
| Pathogens | Proposed therapy | Treatment outcome |
| Brucella spp. | - Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus | Treatment success defined as an antibody titre < 1:60. |

(1) Serum vancomycin concentrations should achieve 10–15 mg/L at pre-dose (trough) level, although some experts recommend to increase the dose of vancomycin to 45–60 mg/kg/day i.v. in 2 or 3 divided doses to reach serum trough vancomycin levels (C_{min}) of 15–20 mg/L as in staphylococcal endocarditis. However, vancomycin dose should not exceed 2 g/day unless serum levels are monitored and can be adjusted to obtain a peak plasma concentration of 30–45 µg/mL 1 h after completion of the i.v. infusion of the antibiotic.

(2) Maximum doses 240 mg/day. High doses are associated with increased risk of nephrotoxicity. Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be < 1 mg/L and post-dose (peak; 1 h after injection) serum concentrations should be ~10–12 mg/L.

(3) In patients with heart failure, the high load of sodium associated with the use of fosfomycin can lead to acute heart failure.

(4) High doses of ertapenem are associated with seizures.

| | | |
|--|--|---|
| | - Rifampin (300–600/24 h) for ≥ 3–6 months orally ⁽¹⁾ | |
| C. burnetii (Q fever agent) | - Doxycycline (200 mg/24 h) plus - Hydroxychloroquine (200–600 mg/24 h) orally (>18 months of treatment) | Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50. |
| Bartonella spp. | - Doxycycline 100 mg/12 h orally for 4 weeks plus - Gentamicin (3 mg/24 h) i.v. for 2 weeks | Treatment success expected in ≥ 90%. |
| Legionella spp. | - Levofloxacin (500 mg/12 h) i.v. or PO for ≥ 6 weeks or - Clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus - Rifampin (300–1200 mg/24 h) | Optimal treatment unknown. |
| Mycoplasma spp. | - Levofloxacin (500 mg/12 h) i.v. or PO for ≥ 6 months | Optimal treatment unknown. |
| T. whipplei (Whipple's disease agent) | - Doxycycline (200 mg/24 h) plus - Hydroxychloroquine (200–600 mg/24 h) orally for ≥ 18 months | Long-term treatment, optimal duration unknown. |

▪ **Outpatient antibiotic therapy for IE:**

- Outpatient parenteral antibiotic treatment (OPAT) **or** step-down outpatient oral antibiotic treatment is used to consolidate antimicrobial therapy once critical infection-related complications are under control and the patient is clinically stable.

(1) Some authors recommend adding gentamicin for the 3 weeks.

- Hence, clinical stability will differentiate IE courses into two phases:
- **Critical phase:** The first phase can last up to 2 weeks of hospital i.v. treatment using standard antibiotics according to specific microorganisms to destroy planktonic bacteria. In this phase, cardiac surgery should be performed if indicated, infected foreign bodies should be removed, and cardiac as well as extracardiac abscesses should be drained.
- **Continuation phase** (beyond 10 days of therapy and 7 days post-surgery), where antibiotic treatment at home with i.v. (OPAT) or oral antibiotic regimens for up to 6 weeks in order to eliminate the dormant (resting) bacteria and prevent relapses.
- TOE is recommended when patient is stable before switching from intravenous to oral antibiotic therapy.
- The patient, and preferably also a caregiver, should be educated in the disease and how to monitor for signs of infection, including daily temperature and other signs of disease progression or complications.
- In addition, regular post-discharge evaluation is required (nurse once per day, physician 1-3 times per week). Regular i.v. catheter inspection and care by a healthcare professional should be provided.

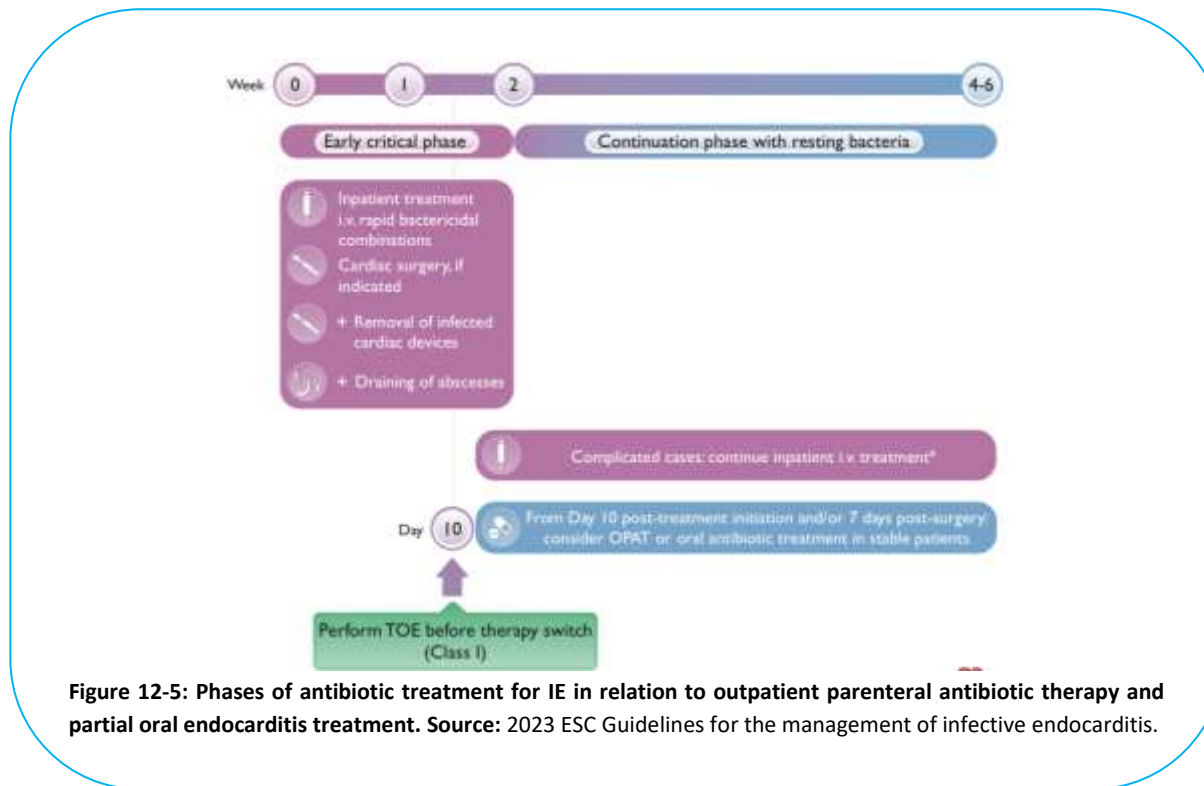
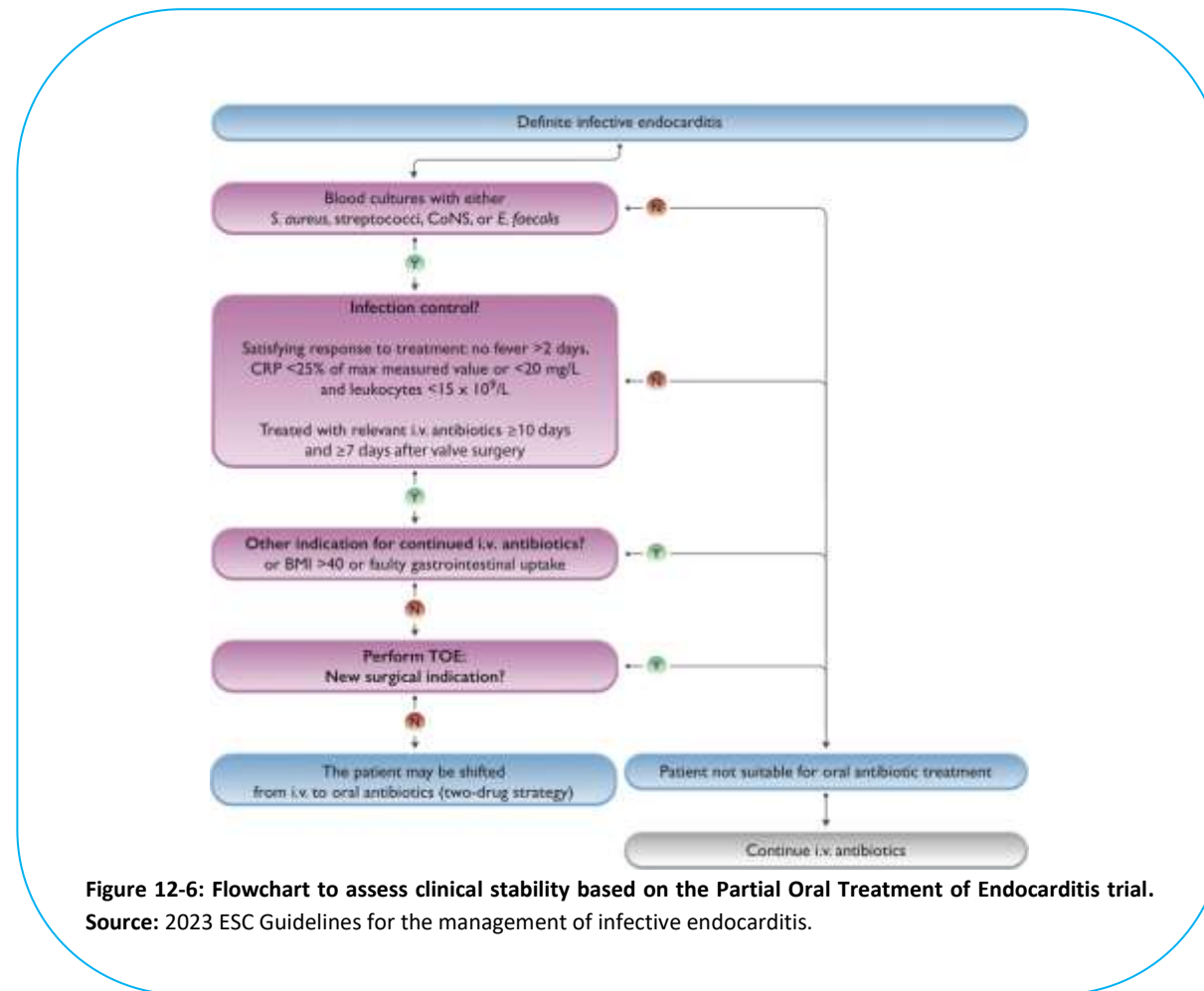


Figure 12-5: Phases of antibiotic treatment for IE in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment. Source: 2023 ESC Guidelines for the management of infective endocarditis.



| Table 12-12: ESC recommendations for outpatient antibiotic treatment of infective endocarditis: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Outpatient parenteral or oral antibiotic treatment should be considered in patients with left-sided IE caused by <i>Streptococcus</i> spp., <i>E. faecalis</i> , <i>S. aureus</i> , or CoNS who were receiving | Ila | A |

| | | |
|---|-----|---|
| <i>appropriate i.v. antibiotic treatment for at least 10 days (or at least 7 days after cardiac surgery), are clinically stable, and who do not show signs of abscess formation or valve abnormalities requiring surgery on TOE.</i> | | |
| <i>Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms ⁽¹⁾, liver cirrhosis (Child-Pugh B or C), severe CNS emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and PWID-related IE.</i> | III | C |

Management of main IE complications:

IE is associated with certain risks and complications that can only be controlled with surgical intervention. Despite the risks of surgery in these patients, current evidence suggests that surgical treatment may generate a survival advantage of up to 20% in the first year. There are three main reasons to undergo surgery in the setting of acute IE: HF, uncontrolled infection, and prevention of septic embolization (particularly, to CNS).

The risk of surgical therapy during the active phase of IE can be significant. It is heavily influenced by pre-existing co-morbidities and current organ function, but should not be limited by one risk factor alone (e.g. age or liver function). There are several scoring systems designed specifically for the setting of IE including the AEPEI score, the STS IE score, the PALSUSE score, the de Feo score, and the ANCLA score, among others.

Timing of surgery:

- Some cases require emergency surgery (within 24 h), irrespective of the pre-operative duration of antibiotic treatment.

(1) Highly difficult-to-treat microorganism: *microorganisms requiring i.v. antibiotic combinations that cannot be administered by means of outpatient parenteral antibiotic treatment or that require strict monitoring of drug levels either in blood or in other fluids owing to their potential toxicity or narrow therapeutic index (e.g. MRSA or vancomycin-resistant enterococci also resistant to alternative drugs such as daptomycin and linezolid, multidrug- or extensively drug-resistant Gram-negative rods, highly penicillin-resistant oral streptococci, fungi other than Candida).*

- A significant proportion of cases require urgent surgery (within 3–5 days).
- A third group requires surgery non-urgently, i.e. within the same hospital admission.
- In cases where the infective component can be completely healed with antibiotics alone, both timing and indications for treatment of residual valve dysfunction follow the VHD guidelines.

Complications of IE:

1. Heart failure:

- Heart failure is the most frequent complication of IE and the main indication for urgent and emergency surgery for IE. Factors associated with increased risk of HF complicating the course of IE include older age, presence of NVE with aortic valve involvement, and high comorbidity.
- Cardiogenic shock can be the first presentation in up to 5% of cases, of which half of such patients develop cardiogenic shock within 72 h of admission for IE.
- Causes of HF in IE include: Leaflet perforation and rupture, as well as mitral chordal rupture. Other less common causes include intracardiac fistulae, interference of the vegetation mass with leaflet opening and closure, or myocardial infarction from vegetations embolizing into the coronary arteries.

• Indications and timing of surgery:

- Emergency surgery should be performed in patients with new-onset NYHA class IV HF symptoms, pulmonary oedema, and/or cardiogenic shock, when considered non-futile intervention.
- Urgent surgery is indicated in patients with milder forms of HF (NYHA class II–III) and severe valve regurgitation or echocardiographic signs of haemodynamic compromise (elevated LVEDP, high LA pressure, or moderate and severe pulmonary hypertension), or large vegetations.
- In patients without haemodynamic compromise, i.v. antibiotic therapy and strict clinical and echocardiographic observation are first indicated, and surgery can be temporarily delayed.

2. Uncontrolled infection:

- Uncontrolled infection is the second most frequent indication for surgery.

- Uncontrolled infection is considered to be present when there is: **(i)** persistent infection or sepsis despite antibiotic therapy; **(ii)** signs of local infection that do not respond to antibiotic therapy; or **(iii)** infection with resistant or very virulent organisms.
- Septic shock ⁽¹⁾ occurs in ~5-10% of patients. Risk factors include *S. aureus* and Gram-negative bacteria, persistent bacteremia, nosocomial acquisition, acute renal failure, DM, CNS emboli, and large vegetations.
- Signs of locally uncontrolled infection include increasing vegetation size, abscess formation, the creation of pseudoaneurysms and/or fistulae, and new AV block.
- **Perivalvular extension:**
 - The incidence of perivalvular extension is 10-30% in NVE with higher incidence in patients with PVE.
 - Perivalvular complications and abscess formation are more frequent in aortic valve than mitral valve IE, and may be higher in patients with bicuspid vs. tricuspid aortic valves.
 - In aortic valve IE, perivalvular extension occurs most frequently in the mitral-aortic intervalvular fibrosa, whereas perivalvular abscesses are usually located posteriorly or laterally in mitral valve IE.
 - Persistent fever and infection, new AV block, chest pain, new heart murmur, recurrent embolism, or HF may indicate perivalvular extension.
 - The diagnosis should be confirmed by TOE. However, mitral annular calcification may obscure small regions of mitral perivalvular extension, particularly in the posterior aspects of the mitral annulus. Cardiac CT has been shown to be an accurate alternative imaging procedure for the evaluation of perivalvular extension, and PET/CT imaging may be particularly helpful in cases of PVE.
- **Indications and timing of surgery:**
 - **Persistent infection:** defined as blood cultures remain positive for > 1 week or persistent sepsis despite appropriate antimicrobials and when other causes of bacteraemia have been excluded.

(1) *Septic shock is defined as vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolaemia.*

- **Locally uncontrolled infection:** if signs of local progression, i.e. increasing vegetation size or perivalvular involvement, are observed during follow-up imaging.
- **Infection with resistant or virulent organisms:** including fungi, *S. aureus* (specifically if early response to antibiotics is not achieved), multiresistant bacteria (e.g. MRSA or vancomycin-resistant enterococci) and, in rare cases, non-HACEK Gram-negative bacteria. The presence of these organisms should lead to discussions within the Endocarditis Team and urgent surgery.

3. Systemic embolism:

- Embolic risk in IE is high, with 20–50% of patients being affected. Embolic events occur in 20–50% of patients secondary to the migration of cardiac vegetations. The brain and spleen are the most frequent sites of embolism for left-sided IE, while pulmonary embolism is frequent in right-sided and pacemaker lead IE. Embolic events may be clinically silent in up to 50% of patients.
- Stroke may be the first clinical manifestation of IE, and is a severe complication that is associated with increased morbidity and mortality.
- Embolic risk is highest the day after therapy initiation, and continuously drop in incidence within the first 2 weeks of antibiotic treatment.
- Several factors are associated with increased risk of embolism including the size and mobility of vegetations (most important), the location of the vegetation on the mitral valve, the increasing or decreasing size of the vegetation under antibiotic therapy, particular microorganisms (especially *S. aureus*, *S. gallolyticus*, and *Candida* spp.), previous embolism, multivalvular involvement, and biological markers.
- Surgery should be considered urgently (within 3-5 days) in such patient.

4. Neurological complications:

- Neurological manifestations may occur before or after the diagnosis of IE is established and recurrent events can also take place later in the course of IE.
- Unexplained fever accompanying a stroke in a patient with valvular disease should trigger the suspicion of IE with blood cultures taken prior to empirical antibiotic therapy.

- *S. aureus* IE is more frequently associated with neurological complications than other microorganisms.
- Prompt diagnosis of IE, early initiation of the antibiotic therapy, and early cardiac surgery in high-risk patients are pivotal to preventing neurological complications. In contrast, antithrombotic/thrombolytic medical therapies are not beneficial.
- The use of anticoagulation in patients with left-sided IE does not seem to have an effect on the risk of stroke, cerebrovascular hemorrhage, or mortality at 10 weeks and, therefore, continuation of anticoagulation in patients with left-sided IE and with a pre-existing indication for the use of anticoagulants is recommended in the absence of other contraindications. Substitution from OAC to heparin in such patients is preferred in case of cerebral bleeding or indication for early surgery.
- Cerebral imaging is mandatory when neurological complications of IE are suspected. Evaluation should include MRI with and without gadolinium, or CT with and without contrast if MRI is not possible. Vascular imaging using CTA or MRA should not be performed routinely, but as screening when infective aneurysm is suspected.
- Catheter angiography should be performed in: **(i)** patients in whom an infective aneurysm was diagnosed on CTA or MRA, **(ii)** patients with an acute brain hemorrhage, or **(iii)** if the suspicion of aneurysm remains despite negative non-invasive techniques, and **(iv)** if mechanical thrombectomy is considered.

5. Infective aneurysms:

- An infective (mycotic) aneurysm is a rare but potentially devastating complication of IE. Infective cerebral aneurysms may be asymptomatic, cause headaches, seizures, or focal symptoms, and may progress to a potentially lethal rupture. They are associated with subarachnoid, intracerebral, and intracranial hemorrhage, particularly when the patient is anticoagulated.
- Digital subtraction angiography (DSA) remains the gold standard test for the detection of infective aneurysms (the sensitivities of CTA and MRA for detecting infective aneurysms are inferior to DSA).
- Treatment options consist of antibiotic treatment with or without endovascular or surgical therapy.

6. Splenic complications:

- Splenic complications range from asymptomatic infarction and abscess formation to splenic rupture.
- Persistent or recurrent fever, abdominal pain, and persistent bacteremia are suggestive for the presence of such complications.
- Patients with suspected splenic complications should be evaluated with ultrasound, abdominal CT, MRI, or PET/CT.

- Treatment includes conservative medical therapy with appropriate antibiotics for splenic infarction or for antibiotic-responsive abscesses. When an abscess is large, splenectomy may be considered, but the timing of splenectomy in relation to heart valve surgery needs careful assessment.

7. Myocarditis and pericarditis:

- Myocarditis will usually present in the form of acute HF and/or ventricular arrhythmias indicating myocardial involvement in the inflammatory process most likely mediated by an immune mechanism.
- The pathophysiological mechanisms most commonly involved in IE-related pericarditis are the extension of inflammation from an infective aneurysm of the aortic root or valve ring abscess, an embolus in an extramural coronary artery, or the rupture of an infective aneurysm.

8. Heart rhythm and conduction disturbances:

- The AV node and His bundle lie in close proximity to the insertion of the septal leaflet of the tricuspid valve, the aortic root (below the non-coronary and right coronary cusps), and the mitral annulus.
- AV block may develop due to paravalvular abscess of these valves, especially of the aortic valve, or as a consequence of valve surgery.
- New-onset AVB caused by local extension of IE (i.e. abscess) is an indication for urgent cardiac surgery.
- Pacemaker implantation should be considered in patients with surgery for valvular endocarditis and complete AVB if one or more of the following risk factors is present: prolonged pre-operative PR and QRS intervals, *S. aureus* infection, presence of aortic root abscess, tricuspid valve involvement, and prior valvular surgery.

9. Musculoskeletal manifestations:

• Osteoarticular IE-related infections:

- Although these lesions are considered an IE-related distal lesion or complication, it is often impossible to determine whether the primary infection is the valve or the osteoarticular infection.
- The rate of IE is 10 times higher in patients with known spondylodiscitis. Therefore, in patients with a definite diagnosis of pyogenic spondylodiscitis and positive blood cultures, TTE/TOE is recommended to rule out IE.

- The most frequent microorganisms associated with spondylodiscitis are *S. aureus*, followed by *Streptococcus* spp., CoNS, and *Enterococcus* spp.
- The most common symptom of spondylodiscitis is back pain.
- MRI should be performed to accurately diagnose spondylodiscitis.
- Antibiotic treatment is appropriate for most cases of spondylodiscitis. The outcome is usually favourable with the 4- to 6-week IE treatment course.
- **Rheumatological manifestations:**
 - Myalgia and back pain are reported in 12–15% of cases. Arthralgia occurs in ~10% of patients, sometimes sequentially affecting several joints. Sacroiliitis is less frequently observed (1% of cases).
 - Rheumatological manifestations and musculoskeletal symptoms show rapid and complete resolution with antibiotics and their presence does not impact on the prognosis of IE.

10. Acute renal failure:

- Acute renal failure is a common complication of IE and is an independent predictor of poor outcome after cardiac surgery. However, acute renal failure should not be a reason to delay cardiac surgery.
- Renal dysfunction may occur due to: **(i)** immune complex and vasculitic glomerulonephritis; **(ii)** renal infarction due to septic emboli; **(iii)** haemodynamic impairment in patients with HF; **(iv)** antibiotic and other drug toxicity (notably related to aminoglycosides, vancomycin, and/or high dose loop diuretics); and **(v)** nephrotoxicity of contrast agents used for diagnostic imaging techniques.
- To reduce the incidence of acute renal failure, nephrotoxic antibiotics should be avoided if possible or, if not possible, serum levels (aminoglycosides and vancomycin) as well as creatinine should be monitored.
- In patients with IE and a reduced glomerular filtration rate, contrast enhanced abdominal ultrasound or MRI are reasonable tests to diagnose embolization as cause of renal function impairment.

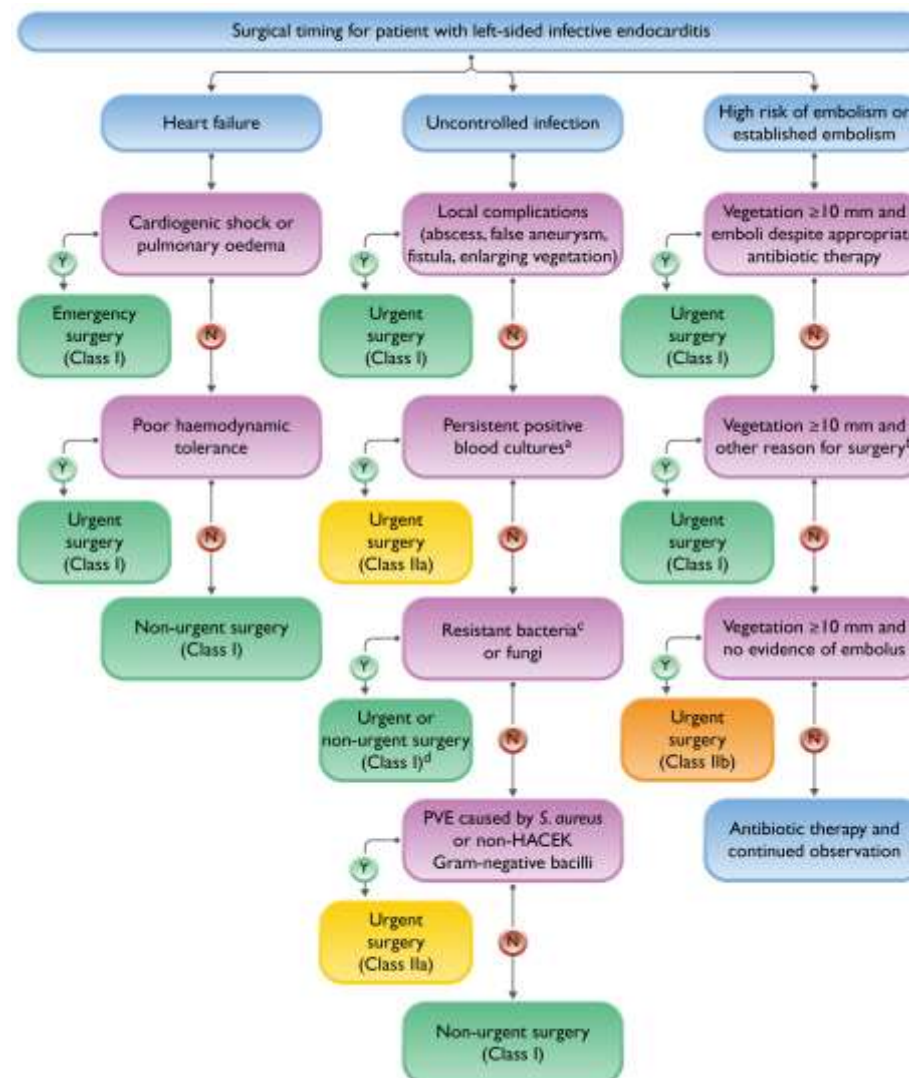


Figure 12-7: Proposed surgical timing for infective endocarditis. HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella. **Surgery timing:** emergency, within 24 h. Urgent, within 3–5 days. Non-urgent, within same hospital admission. **A)** Despite appropriate antibiotic therapy for >1 week and control of septic embolic foci. **B)** E.g. patients with significant valvular dysfunction that is, or is not, a direct result of endocarditis process. **C)** *S. aureus* (methicillin resistant and non-methicillin resistant), vancomycin-resistant enterococci, non-HACEK Gram-negative bacteria and fungi. **D)** Urgent for *S. aureus*, non-urgent for others. **Source:** 2023 ESC Guidelines for the management of infective endocarditis.

Table 12-13: ESC recommendations for management of infective endocarditis complications:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Heart failure: | | |
| <i>Emergency surgery (within 24 h) is recommended in aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary oedema or cardiogenic shock.</i> | I | B |
| <i>Urgent surgery (within 3–5 days) is recommended in aortic or mitral NVE or PVE with severe acute regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor hemodynamic tolerance.</i> | I | B |
| Uncontrolled infection: | | |
| <i>Urgent surgery (within 3–5 days)</i> | | |
| ○ <i>is recommended in locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation, prosthetic dehiscence, new AVB).</i> | I | B |
| ○ <i>should be considered in IE with persistently positive blood cultures > 1 week or persistent sepsis despite appropriate antibiotic therapy and adequate control of metastatic foci.</i> | IIa | B |
| ○ <i>should be considered in PVE caused by S. aureus or non-HACEK Gram-negative bacteria.</i> | IIa | C |
| <i>Urgent (within 3–5 days) or non-urgent surgery (within same hospital admission) is recommended in IE caused by fungi or multiresistant organisms according to the hemodynamic condition of the patient.</i> | I | C |
| Prevention of embolism: | | |
| <i>Urgent surgery (within 3–5 days) is recommended in:</i> | | |
| ○ <i>aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after one or more embolic episodes despite appropriate antibiotic therapy.</i> | I | B |

| | | |
|--|-----|---|
| ○ IE with vegetation ≥ 10 mm and other indications for surgery | I | C |
| Urgent surgery (within 3–5 days) may be considered in aortic or mitral IE with vegetation ≥ 10 mm and without severe valve dysfunction or without clinical evidence of embolism and low surgical risk. | IIb | B |
| Neurological complications: | | |
| Brain CT or MRA is recommended in patients with IE and suspected infective cerebral aneurysms. | I | B |
| Neurosurgery or endovascular therapy is recommended for large aneurysms, those with continuous growth despite optimal antibiotic therapy, and ruptured intracranial infective cerebral aneurysms. | I | C |
| If non-invasive techniques are negative and the suspicion of infective aneurysm remains, invasive angiography should be considered. | IIa | B |
| In embolic stroke, mechanical thrombectomy may be considered if the expertise is available in a timely manner. | IIb | C |
| Thrombolytic therapy is not recommended in embolic stroke due to IE. | III | C |
| Musculoskeletal manifestations: | | |
| MRI or PET/CT is recommended in patients with suspected spondylodiscitis and vertebral osteomyelitis complicating IE. | I | C |
| TTE/TOE is recommended to rule out IE in patients with spondylodiscitis and/or septic arthritis with positive blood cultures for typical IE microorganisms. | I | C |
| More than 6-week antibiotic therapy should be considered in patients with osteoarticular IE-related lesions caused by difficult-to-treat microorganisms, such as <i>S. aureus</i> or <i>Candida</i> spp., and/or complicated with severe vertebral destruction or abscesses. | IIa | C |

Pacemaker implantation in patients with complete AV block and IE:

*Immediate epicardial pacemaker implantation should be considered in patients undergoing surgery for valvular IE and complete AVB if one of the following predictors of persistent AVB is present: pre-operative conduction abnormality, *S. aureus* infection, aortic root abscess, tricuspid valve involvement, or previous valvular surgery.*

IIa

C

Surgical therapy:

- **Pre-operative and peri-operative management:**

- **Coronary angiography:** Classically, pre-operative coronary angiography is recommended for men > 40 years, post-menopausal women, and in those with one or more cardiovascular risk factors or history of CAD. The presence of aortic valve vegetations may preclude invasive coronary angiography due to the risk of iatrogenic embolization. Alternatively, coronary CTA can be used to rule out significant CAD.
- **Extracardiac infection:** Extracardiac foci may be treated prior to valve surgery, during the valve operation, or post-operatively, dependent on the urgency of cardiac surgery. Regardless of the timing of intervention, infective foci need to be eradicated before completion of antibiotic therapy in order to avoid cardiac valve reinfection.
- **Intra-operative considerations:**
 - Extent of infection, stability of known vegetations, re-assessment of previously uninvolved heart valves, and biventricular function are performed with intra-operative TOE. Intra-operative TOE post-surgical repair is mandatory to determine the immediate result and establish baseline for follow-up comparisons.
 - Although the pharmacokinetics of antibiotic therapy is altered during cardio-pulmonary bypass, adjustment of doses is rarely required.
 - Intra-operative bleeding management is often complicated by marked coagulopathy in patients with IE, particularly those undergoing surgery during persistent sepsis.

- The management of hypotension and vasoplaegia is particularly challenging in patients presenting with septic shock, and accompanying vasoplaegia tends to worsen significantly during CPB. Norepinephrine is frequently used as first-line therapy for septic shock, followed by vasopressin or terlipressin in cases of resistant vasoplaegia. Methylene blue may be used as a rescue agent in patients who are unresponsive to these measures, but mortality rates are high for such patients.

Table 12-14: ESC recommendations for pre-operative coronary anatomy assessment in patients requiring surgery for IE:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In haemodynamically stable patients with aortic valve vegetations who require cardiac surgery and are high risk for CAD, a high-resolution multislice coronary CTA is recommended.</i> | I | B |
| <i>Invasive coronary angiography is recommended in patients requiring heart surgery who are high risk for CAD, in the absence of aortic valve vegetations.</i> | I | C |
| <i>In emergency situations, valvular surgery without pre-operative coronary anatomy assessment regardless of CAD risk should be considered.</i> | IIa | C |
| <i>Invasive coronary angiography may be considered despite the presence of aortic valve vegetations in selected patients with known CAD or at high risk of significant obstructive CAD.</i> | IIb | C |

- **Surgical approach and techniques:**

- Aortic valve replacement is usually required for aortic IE. Aortic valve repair is very uncommon in the acute situation but may be performed for isolated aortic regurgitation after healed endocarditis.
- In mitral IE, leaflet perforations with preserved free margin and chordae tendinae may be treated with patch repair, particularly in the setting of subacute or healed IE.
- The use of patches to cover abscess cavities and prevent extensive resection and reconstruction is discouraged in aortic root IE as it may be associated with recurrences, periprosthetic leaks, and pseudoaneurysm formation. After exclusion from the circulation, abscess and pseudoaneurysm cavities are left to drain into the pericardial cavity.

- Features favouring a non-mechanical valve substitute in the setting of surgery for acute IE:
 - Early surgery after a recent ischaemic stroke.
 - Evidence of intracranial bleeding.
 - Woman of childbearing age.
 - High likelihood of prolonged mechanical circulatory support.
 - Advanced age or frailty.
 - Poor or unknown medical compliance.
 - Expected complicated and prolonged post-operative course.
 - Patient preference.
- **Timing of surgery after ischemic and hemorrhagic stroke:**
 - For patients who have suffered a neurological injury, neurological exacerbation may occur during surgery or early post-operatively due to the altered physiology conditions during and immediately after cardiac repair. The risk of neurological exacerbation during surgery needs to be balanced against that of delaying a cardiac operation.
 - The risk of post-operative hemorrhagic conversion after pre-operative stroke is 2–7%. When hemorrhagic transformation occurs, it is associated with high mortality (40%) and may require rescue neurointerventional or neurosurgical treatment to control bleeding or allow cerebral decompression by means of craniectomy.
 - The timing of surgery after intracranial hemorrhage is controversial.

Table 12-15: ESC recommendations for indications and timing of cardiac surgery after neurological complications in active IE:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|---------------------|---------------------|
| <i>After a transient ischemic attack, cardiac surgery, if indicated, is recommended without delay.</i> | I | B |

| | | |
|--|------------|----------|
| <i>After a stroke, surgery is recommended without any delay in the presence of HF, uncontrolled infection, abscess, or persistent high embolic risk, as long as coma is absent and the presence of cerebral hemorrhage has been excluded by cranial CT or MRI.</i> | I | B |
| <i>Following intracranial hemorrhage, delaying cardiac surgery > 1 month, if possible, with frequent re-assessment of the patient's clinical condition and imaging should be considered.</i> | IIa | C |
| <i>In patients with intracranial hemorrhage and unstable clinical status due to HF, uncontrolled infection or persistent high embolic risk, urgent or emergency surgery should be considered weighing the likelihood of a meaningful neurological outcome.</i> | IIa | C |

- **Post-operative complications:** Post-operative management of patients with IE may be challenging due to pre-operative multiorgan involvement and often complex surgical procedures. The risk of in-hospital mortality associated with IE surgery remains high (10–20%), particularly in patients >75 years of age, usually due to co-morbidities and complications of IE. The most frequent serious post-operative complications are coagulopathy requiring extensive use of blood products and clotting factors, re-exploration of the thorax due to bleeding/tamponade, hemodialysis, stroke, or cerebral hemorrhagic transformation of prior cerebrovascular lesions, low cardiac output syndrome, respiratory complications and tracheostomy, prolonged hospital stay, and need for a permanent pacemaker.
- **Management of antithrombotic therapy after surgery:** The management of antithrombotic therapy early after surgery for IE may need to be altered when compared with non-IE clinical scenarios. This is mainly due to known increased risk of intracranial hemorrhage after cerebral embolism. Restrictive or tailored use of antiplatelet and antithrombotic agents after surgery are key to avoid further complications, which is more feasible in patients who received bioprosthetic valve prostheses or valve repair operations than after mechanical valve replacement surgery.

Follow-up and long-term prognosis:

Following in-hospital treatment, patients should be followed-up for the occurrence of main post-discharge complications, including recurrence of infection, HF, need for valve surgery or additional intervention, stroke, need for renal replacement therapy, psychological complications, and death.

- **Recurrences: relapses and reinfections:**

The risk of recurrence (which includes relapses and reinfections) among survivors of IE varies significantly between studies, ranging from 2% to 9%. **Relapse** refers to a repeat episode of IE caused by the same microorganism and represents a failure of treatment due to insufficient duration of initial treatment, sub-optimal choice of initial antibiotics, or a persistent focus of infection. **Reinfection** is related to patients' clinical and immunological profiles, describes an infection caused by a different microorganism usually more than 6 months after the initial episode, and is associated with worse outcome. Relapse should be treated with i.v. antibiotics for an additional 4–6 weeks, depending on the causative microorganism and its susceptibility, and cardiac surgery should be considered.

- **Factors associated with an increased rate of relapse:**

- Inadequate antibiotic treatment (agent, dose, duration).
- Resistant microorganisms, i.e. *Brucella* spp., *Legionella* spp., *Chlamydia* spp., *Mycoplasma* spp., *Mycobacterium* spp., *Bartonella* spp., *Coxiella Burnetii*, fungi.
- Polymicrobial infection in people who inject drugs.
- Empirical antimicrobial therapy for BCNIE.
- Periannular extension.
- Prosthetic valve endocarditis.
- Persistent metastatic foci of infection (abscesses).
- Resistance to conventional antibiotic regimens.
- Positive valve culture.

- Persistence of fever at the seventh postoperative day.
- Chronic dialysis.
- Poor oral hygiene.
- **First year follow-up:**
 - To monitor the risk of secondary HF, an initial clinical evaluation, baseline TTE and inflammatory markers (i.e. WBC, CRP, procalcitonin) should be performed at the completion of antimicrobial therapy and repeated if a change in the clinical condition occurs. Due to the increased risk of relapse for virulent microorganisms, blood cultures are also encouraged within the first week after finishing treatment.
 - Clinical re-assessment should be performed one or more times in the first year and yearly thereafter. The need for late valve surgery is relatively low, ranging from 3% to 11%.
 - Cardiac rehabilitation, including physical exercise training and patient education, has been shown to be safe and feasible in stable patients at a minimum of 2 weeks after surgery for left-sided IE.
 - Good oral health maintenance, preventive dentistry, and advice about skin hygiene, including advice on tattoos and skin piercing, are mandatory.
 - In PWID patients, follow-up care should include a strategy for addiction treatment, involve relevant addiction specialists before hospital discharge, and possibly including medication for opioid-use disorder.
- **Long-term prognosis:** Contemporary long-term survival rates after the completion of IE treatment are estimated to be ~85-90% and 70-80% at 1 and 5 years, respectively. The main predictors of long-term mortality are age, co-morbidities, PWID, double valve infection, recurrences of IE, and HF, especially when cardiac surgery cannot be performed.

Antithrombotic therapy in IE:

- Infective endocarditis by itself is not an indication for antithrombotics or anticoagulants, and bleeding complications or stroke may in contrast justify discontinuation or interruption of such therapies.

- For patients with IE and stroke, thrombolytic therapy is not recommended. However, thrombectomy may be considered in selected cases with large vessel occlusion.
- Bridging with LMWH/unfractionated heparin instead of oral anticoagulants should be considered early on in the IE course, especially for patients in whom surgery is indicated.

Table 12-16: ESC recommendations for the use of antithrombotic therapy in infective endocarditis:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Interruption of antiplatelet or anticoagulant therapy is recommended in the presence of major bleeding (including intracranial hemorrhage).</i> | I | C |
| <i>In patients with intracranial hemorrhage and a mechanical valve, reinitiating unfractionated heparin should be considered as soon as possible following multidisciplinary discussion.</i> | IIa | C |
| <i>In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated heparin under close monitoring should be considered in cases where indication for surgery is likely (e.g. <i>S. aureus</i> IE).</i> | IIa | C |
| <i>Thrombolytic therapy is not recommended in patients with IE.</i> | III | C |

Management of specific situations:

Right-sided infective endocarditis

- Right-sided IE accounts for ~5–10% of patients with IE.
- Risk factors include patients with CHD, indwelling catheters, and CIED, as well as immunocompromised and PWID patients. Of these, patients with indwelling vascular catheters have the worst prognosis.
- The most common microorganism causing right-sided IE is *S. aureus*.

- The tricuspid valve is much more commonly infected than the pulmonary valve. Right-sided IE may also involve non-functional embryonic remnants of the right atrium (e.g. Eustachian valve).
- **Endocarditis in people who inject drugs (PWID):** Repeat i.v. injections result in contaminated particles that reach the tricuspid valve and right-heart chambers and can also lead to infection of left-heart structures, which is associated with worse prognosis. PWID patients also have an increased rate of HIV and hepatitis. The majority of right-sided IE in PWID can be treated successfully with antibiotic therapy. It is associated with higher mortality rates (even when surgery is required, probably due to the young patient age) and increased rate of IE recurrence, particularly in the first 6 months post-surgery.
- **Diagnosis and complications:**
 - Right-sided IE patients present with fever, bacteremia, and pulmonary complaints (i.e. cough, chest pain, or hemoptysis). Right-sided HF may also occur due to tricuspid or pulmonary regurgitation, or to pulmonary hypertension induced by multiple pulmonary septic emboli.
 - Adequate evaluation of the tricuspid valve may be performed with TTE, due to the anterior location of the valve and the large vegetations frequently observed in right-sided IE. TOE is frequently required for evaluation of the pulmonary valve or in patients with indwelling venous catheters or intracardiac devices.
 - CT is useful to identify concomitant pulmonary disease, including infarcts and abscess formation.
- **Prognosis:** Right-sided IE is generally more benign than left-sided IE and can be medically managed in ~90% of cases. Right-sided IE in immunocompromised patients, particularly fungal infections, has a very poor prognosis.
- **Treatment:**
 - **Antimicrobial therapy:**
 - *S. aureus* and CoNS are the most common cause of right-sided IE, with *S. aureus* predominating in PWID and CoNS being more common in patients with indwelling devices. Antifungals may be necessary in selected PWID, particularly if immunocompromised.
 - The standard 4–6-week regimen should be used in the majority of patients. Two-week treatment with oxacillin (or cloxacillin) without gentamicin is effective when:

- (i) MSSA is the causative organism;
 - (ii) There is good clinical and microbiological response to treatment (> 96 h);
 - (iii) The vegetation size is ≤ 20 mm; and
 - (iv) There is an absence of metastatic sites of infection or empyema and cardiac or extracardiac complications, prosthetic valve or left-sided valve infection, and severe immunosuppression.
- **Surgery:**
 - Tricuspid valve repair is more frequently performed than replacement.
 - When valve replacement for right-sided IE is required, bioprostheses are frequently preferred due to concerns with the management and risks of lifelong anticoagulation, especially in PWID.
 - Indications for surgical treatment of right-sided IE:
 - A. Persistent bacteraemia after at least 1 week of appropriate antibiotic therapy.
 - B. RV dysfunction secondary to acute severe tricuspid regurgitation non-responsive to diuretics.
 - C. Respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.
 - D. Involvement of left-sided structures; and
 - E. Large residual tricuspid vegetations (> 20 mm) after recurrent pulmonary emboli. An isolated vegetation is not an indication for surgery. Patients with residual large vegetations frequently present with right-heart and/or respiratory failure, as well as persistent sepsis.
 - Prophylactic placement of permanent epicardial leads should be performed at the time of tricuspid valve surgery for right-sided IE, particularly if heart block is present in the operating room to prevent damage of a replaced valve during subsequent transvenous lead displacement and to lower the risk of reinfection.
 - Percutaneous aspiration of large vegetations. The main goals have been debulking of septic intracardiac masses, reducing the infectious load, and achieving clinical stability.

Table 12-17: ESC recommendations for surgical treatment of right-sided infective endocarditis:

Recommendations

Class Level

| | | |
|---|-----|---|
| Surgery is recommended in patients with right-sided IE who are receiving appropriate antibiotic therapy for the following scenarios: | | |
| ○ <i>RV dysfunction secondary to acute severe TR non-responsive to diuretics.</i> | I | B |
| ○ <i>Persistent vegetation with respiratory insufficiency requiring ventilatory support after recurrent pulmonary emboli.</i> | I | B |
| ○ <i>Large residual tricuspid vegetations (> 20 mm) after recurrent septic pulmonary emboli.</i> | I | C |
| ○ <i>Patients with simultaneous involvement of left-heart structures.</i> | I | C |
| <i>Surgery should be considered in patients with right-sided IE who are receiving appropriate antibiotic therapy and present persistent bacteraemia/sepsis after at least 1 week of appropriate antibiotic therapy.</i> | IIa | C |
| <i>Tricuspid valve repair should be considered instead of valve replacement, when possible.</i> | IIa | B |
| <i>Prophylactic placement of an epicardial pacing lead should be considered at the time of tricuspid valve surgical procedures.</i> | IIa | C |
| <i>Debulking of right intra-atrial septic masses by aspiration may be considered in selected patients who are high risk for surgery.</i> | IIb | C |

Prosthetic valve endocarditis (PVE)

PVE is the most severe form of IE and occurs in 1–6% of patients with valve prostheses. PVE accounts for 20–30% of all cases of IE, and may be more common after biological than after mechanical valve.

- **Pathophysiology:**

- PVE with an onset in the peri-operative period involves mainly *S. aureus*, *Staph. epidermidis*, or nosocomial microorganisms, such as Gram-negative pathogens or fungi. Late PVE more commonly mimics the pattern of NVE, which is mostly represented by streptococcal and staphylococcal infections.
- *S. aureus* is more commonly observed in patients with mechanical valves, while alpha-haemolytic streptococci, enterococci, and CoNS are more common in patients with bioprosthetic valves.
- PVE due to *Mycobacterium chimaera* can result from contaminated CPB heater-cooler systems. Such infections present many months after the index operation and can therefore be challenging to identify, and are associated with high mortality.
- **Diagnosis:**
 - As in NVE, diagnosis of PVE is based mainly on the results of echocardiography and blood cultures.
 - TOE is mandatory in suspected PVE. Identification of a new periprosthetic leak is a major criterion of IE and urges additional imaging modality (e.g. nuclear techniques, esp. [18F]FDG-PET/CT) to confirm.
- **Prognosis:**
 - Compared with NVE, PVE is associated with increased in-hospital mortality and morbidity as well as reduced long-term survival.
 - Several factors have been associated with poor prognosis in PVE, including older age, DM, healthcare-associated infections, and early PVE. Among the different causative organisms, staphylococcal or fungal infection seem to be more aggressive, whereas enterococcal infections are associated with similar mortality but higher recurrence rates. Haemodynamic instability, multivalvular involvement as well as involvement of the aortomitral fibrosa have been associated with worse outcomes.
- **Treatment:**

Surgical strategy is recommended for PVE in high-risk subgroups (i.e. PVE complicated with HF, severe prosthetic dysfunction, abscess, or persistent fever).

Conversely, patients with uncomplicated non-staphylococcal late PVE can be managed conservatively.

Table 12-18: ESC recommendations for prosthetic valve endocarditis:

Recommendations

Class Level

Surgery is recommended for early PVE (within 6 months of valve surgery) with new valve replacement and complete debridement.

I

C

Transcatheter prosthetic valve endocarditis

- **Endocarditis following TAVI:**

- The incidence of IE post-TAVI ranges from 0.3 to 1.9 per 100 patient-years, which is similar to post-SAVR.
- The risk of IE is higher within the first year following the procedure, and particularly within the initial 3 months. A similar IE rate has been reported irrespective of transcatheter valve type.
- **Predisposing factors:** younger age, male gender, renal dysfunction, and significant residual AR.
- **Diagnosis:**
 - The diagnosis of IE post-TAVI is challenging due to: (i) The stent frame of transcatheter valves has a much higher amount of metal surrounding the valve leaflets compared with surgical prostheses, and (ii) characteristics of TAVI patients (frequently elderly with multiple co-morbidities).
 - Enterococci and *S. aureus* are the two most common microorganisms in IE post-TAVI.
 - Regarding TOE in patients with suspected IE post-TAVI: (i) no vegetations are detected in 38–60% of cases; (ii) vegetations are located in the stent frame (and not on the valve leaflets) in 12% of cases, and (iii) the vegetations are located outside the transcatheter valve in about one-third of cases, mainly at the level of the mitral valve.
 - Nuclear imaging or CT have been useful to diagnose IE post-TAVI.
- **Prognosis:** About two-thirds of patients with IE post-TAVI exhibit at least one complication, especially acute kidney injury and HF. The in-hospital and 30-day mortality rates are very high (16-36%).
- **Treatment:** Antimicrobial therapy for IE post-TAVI is similar to that of PVE. Similar to surgical PVE, cardiac surgery is considered the best option in the presence of IE complications, particularly severe prosthetic failure or HF, but is infrequently performed.

In cases with healed IE and valve prosthesis dysfunction, repeat transcatheter therapy (valve-in-valve procedure) can be performed in select patients. Such interventions should be performed at least 1–3 months after the healed endocarditis episode and following a negative follow-up TOE.

- **Endocarditis following transcatheter pulmonary valve implantation (TPVI):**

- The incidence of IE post- TPVI ranges from 1.6 to 4.0 per 100 patient-years, which seems to be higher than that reported following surgical pulmonary valve interventions.
- **Predisposing factors:** younger age, a previous history of IE, and a higher transvalvular residual gradient.
- *S. aureus* and oral group streptococci are the most common microorganisms causing IE post-TPVI.
- **Diagnosis:** The diagnosis may be challenging, and the use of intracardiac echocardiography and [18F]FDG-PET/CT has been shown to be useful in cases with a clinical suspicion and negative TTE/TOE.
- **Prognosis:** The mortality rate related to the IE episode ranges from 0-11%. This rate is much lower compared with TAVI patients (due to younger and less co-morbid characteristics of the TPVI population).

Cardiac implanted electronic device (CIED)-related IE

- **Definition:** Evidence of CIED infection with clinical signs of pocket infection and/or imaging findings (lead vegetations, positive FDG-PET on the generator/leads etc.) which fulfil the criteria for valvular IE.
- **Pathophysiology:** CIED-related IE occurs by two mechanisms:
 - I. Local infection usually results from bacterial flora from the patient's skin that is introduced into the pocket at the time of incision despite surgical preparation.
 - II. Seeding via bacteraemia from a distant focus (less frequent).
- The most frequent agents identified with bacteraemia in CIED infection are *S. aureus* and CoNS. CoNS are most frequently the cause of chronic pocket infection.
- **Prophylaxis:**

- Prevention of CIED infection at implantation includes: **(i)** correction of modifiable risk factors (e.g. postponing the procedure in cases of fever or signs of infection and avoiding temporary pacing). **(ii)** Routine administration of prophylactic systemic antibiotics within 1 h of incision.
- Haematoma is a major contributor to risk of infection, and all measures should be taken to avoid this complication. Another risk factor is a revision with re-opening of the pocket (e.g. for lead repositioning).
- Antibiotic prophylaxis to prevent CIED-related IE before interventions, such as dental, respiratory, gastrointestinal, or genitourinary procedures, is not warranted as the risk is very low.
- **Diagnosis:**
 - Clinical presentation of CIED-associated IE is similar to valvular IE with patients frequently presenting with fever, chills, and embolic events. Signs of pocket infection (swelling, tenderness, erythema, purulent discharge etc.) may or may not be present. Suspicion of CIED-associated IE should be particularly high in the event of *S. aureus* bacteraemia.
 - TTE and TOE are both recommended in the case of suspected CIED-related IE. However, the absence of vegetations does not rule out IE, as these may be present on extracardiac segments of the lead.
 - Repeating TTE and/or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of CIED-related IE remains high.
 - A chest X-ray or CT should be performed to evaluate the presence of pulmonary complications.
- **Management:**
 - Early and complete removal of all parts of the system, combined with initial empirical antibiotic therapy directed at MRSA and Gram-negative bacteria, while awaiting identification of the pathogen.
 - Large vegetations may be aspirated percutaneously before lead extraction to reduce risk of embolization.
 - Reimplantation should be performed at a site distant from that of the previous generator, and delayed until signs and symptoms of local and systemic infection have resolved and blood cultures are negative for at least 72 h after extraction in the absence of vegetations or ‘ghosts’ (fibrous remnants after lead extraction, which have been associated with death and

reinfection), or after 2 weeks of negative blood cultures if vegetations were visualized. No part of the removed CIED system should be reimplanted.

- For patients with a high risk of SCD, a wearable defibrillator is an option as a bridge to reimplantation. In pacemaker-dependent patients, an active-fixation lead may be introduced via the internal jugular vein and connected to an external pacemaker for up to 4–6 weeks, thereby preserving the contralateral side for definitive device reimplantation.

| Table 12-19: ESC recommendations for Cardiac device-related infective endocarditis: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Antibiotic prophylaxis covering S. aureus is recommended for CIED implantation.</i> | I | A |
| <i>TTE and TOE are both recommended in case of suspected CIED-related IE to identify vegetations.</i> | I | B |
| <i>Obtaining at least three sets of blood cultures is recommended before prompt initiation of empirical antibiotic therapy for CIED infection, covering methicillin-resistant staphylococci and Gram-negative bacteria.</i> | I | C |
| System extraction: | | |
| <i>Complete system extraction without delay is recommended in patients with definite CIED-related IE under initial empirical antibiotic therapy.</i> | I | B |
| <i>Complete CIED extraction should be considered in case of valvular IE, even without definite lead involvement, taking into account the identified pathogen and requirement for valve surgery.</i> | IIa | C |
| <i>In cases of possible CIED-related IE with occult Gram-positive bacteraemia or fungaemia, complete system removal should be considered in case bacteraemia/fungaemia persists after a course of antimicrobial therapy.</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>In cases of possible CIED-related IE with occult Gram-negative bacteraemia, complete system removal may be considered in case of persistent/relapsing bacteraemia after a course of antimicrobial therapy.</i> | IIb | C |
| <i>Removal of CIED after a single positive blood culture, with no other clinical evidence of infection, is not recommended.</i> | III | C |
| Antibiotics duration: | | |
| <i>Extension of antibiotic treatment of CIED-related endocarditis to (4–6) weeks following device extraction should be considered in the presence of septic emboli or prosthetic valves.</i> | IIa | C |
| <i>In non-S. aureus CIED-related endocarditis without valve involvement or lead vegetations, and if follow-up blood cultures are negative without septic emboli, 2 weeks of antibiotic treatment may be considered following device extraction.</i> | IIb | C |
| Reimplantation: | | |
| <i>If CIED reimplantation is indicated after extraction for CIED-related IE, it is recommended to be performed at a site distant from the previous generator, as late as possible, once signs and symptoms of infection have abated and until blood cultures are negative for at least 72 h in the absence of vegetations, and negative for at least 2 weeks if vegetations were visualized.</i> | I | C |
| <i>Use of an antibiotic envelope may be considered in select high-risk patients undergoing CIED reimplantation to reduce risk of infection.</i> | IIb | B |

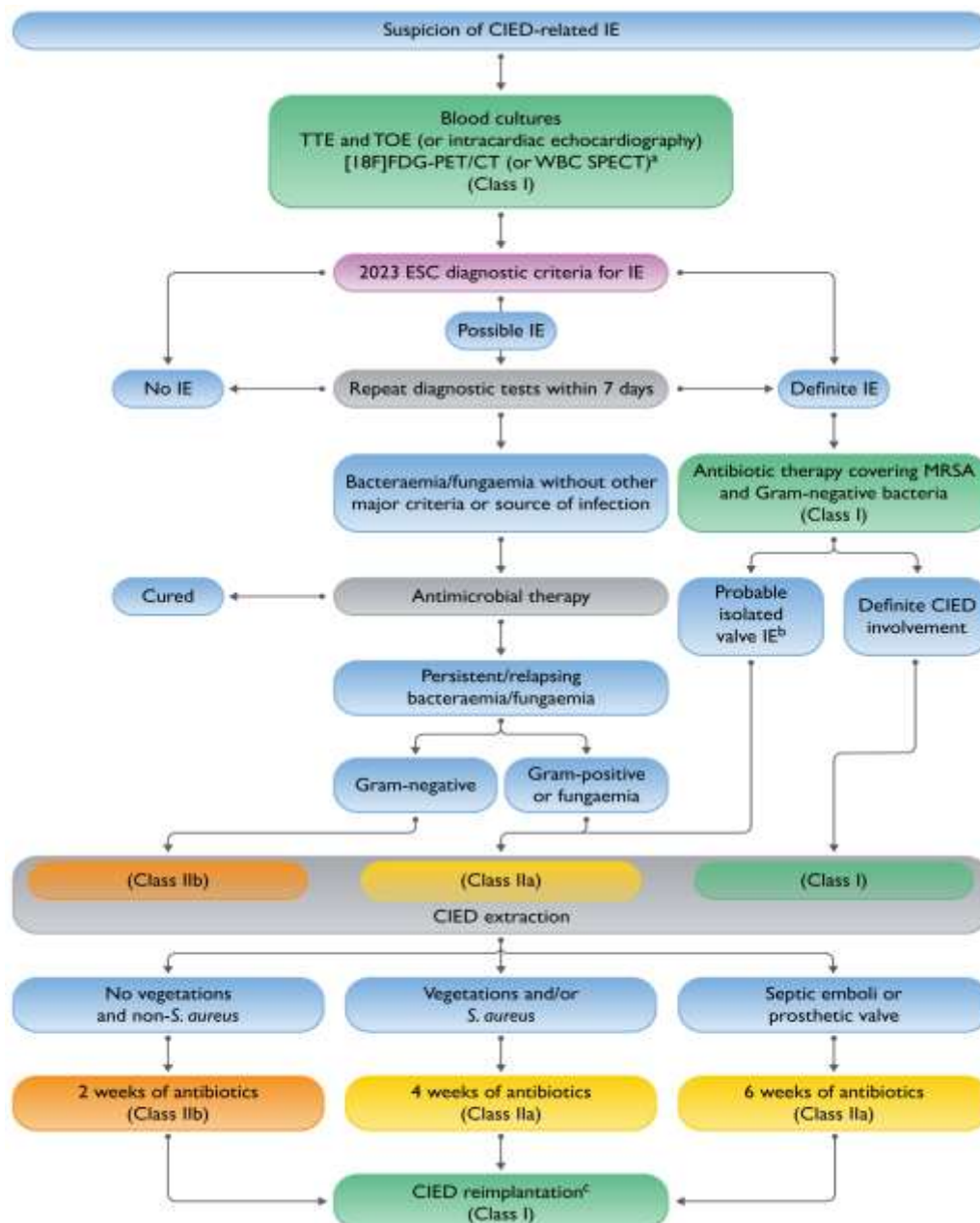


Figure 12-8: Management of cardiovascular implanted electronic device-related infective endocarditis. A) no signs of pocket infection and negative TOE. B) Taking into account the identified pathogen, procedural risk, and requirement for valve surgery. C) At a distant site and postponed as long as possible (until signs and symptoms of infection have resolved and blood cultures are negative for >72 h in the absence of vegetations and /or 'ghosts', or otherwise after > 2 weeks of negative blood cultures). **Source:** 2023 ESC Guidelines for the management of infective endocarditis

Non-bacterial thrombotic endocarditis (NBTE)

- NBTE is a rare condition with an incidence varying from 1.1% to 1.6% which occurs in patients with a predisposing factor and/or a hypercoagulable state, such as SLE, APLs (Libman–Sacks endocarditis), cancer (marantic endocarditis), disseminated intravascular coagulation (DIC), or various other chronic diseases (tuberculosis or autoimmune disease).
- Increased production of coagulation factors, of cytokines, and high tissue factor expression are potential mechanisms underlying NBTE in cancer patients.
- Among the patients with malignancies, the three most frequent cancers were lung adenocarcinoma, breast, and pancreatic cancer.
- The mitral valve was more often affected (62%) than the aortic valve (24%).
- **Diagnosis:** The diagnosis of NBTE remains challenging and should be suspected in patients presenting with systemic embolization and a predisposing factor (i.e. cancer, APLs, SLE).
- Stroke is the most frequent presentation (60%), while HF is observed in 21% and ACS in 7% of patients.
- TTE was able to confirm the diagnosis in 45% of patients. Libman–Sacks vegetations may present with various shapes (sessile, tubular, or coalescent), various levels of echogenicity (heterogeneously or homogeneously), could be nodular or protuberant, are generally located near the leaflet's edge of coaptation, and frequently have extensions to the mid and basal portions of the leaflet. They are rarely associated with valve dysfunction and never with valve perforation, which is an important method of differentiating from bacterial IE.
- The treatment of the underlying cause (i.e. SLE or cancer) is crucial to prevent recurrent NBTE. Anticoagulant treatment should be considered in all patients. There are no data to support the use of direct oral anticoagulants in NBTE. The role of surgery is controversial. However, surgery should be considered in patients with severe valve dysfunction or with large vegetations.

References and suggested readings:

- Delgado V, Ajmone Marsan N, de Waha S, et al. 2023 ESC Guidelines for the management of endocarditis. Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM). European Heart Journal.
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Chapter 13:

Rheumatic fever

Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. Initiated by a pharyngeal infection with group A beta-hemolytic streptococci (GAS) and following a latent period of approximately 2 to 3 weeks, the illness is characterized by acute inflammation of the heart, joints, skin, subcutaneous tissue, and central nervous system. Pathologically, the inflammatory process causes damage to collagen fibrils and connective tissue ground substance (i.e., fibrinoid degeneration), and thus rheumatic fever is classified as a *connective tissue or collagen vascular disease*.

Pathogenesis:

- Streptococcus pyogenes infection → activation of the innate immune system leading to antigen presentation to T cells.
- GAS pharyngitis triggers an autoimmune response to epitopes in the organism that cross-react with similar epitopes in the heart, brain, joints and skin (*molecular mimicry*, type II hypersensitivity).
- This response leads to the clinical features of rheumatic fever. Recurrent episodes of rheumatic fever lead to RHD
- Referring to the fleeting arthritis and damaging carditis characteristic of rheumatic fever, the French physician Ernst-Charles Lasègue famously said in 1884, “*Pathologists have long known that rheumatic fever licks at the joints, but bites at the heart.*”
- Aschoff bodies describes the granulomatous nodules found in rheumatic heart fever.

Diagnosis:

Table 13-1: 2015 AHA-Revised Jones Criteria for Diagnosis of Rheumatic Fever

Evidence of recent streptococcal infection:

- *Raised or rising streptococci antibodies*
- *Positive throat swab*
- *Positive rapid group A streptococcal antigen test*

Major criteria:

1. *Erythema marginatum*
2. *Subcutaneous nodules*
3. *Arthritis: (only Polyarthritis is considered in low-risk population) ⁽¹⁾*
4. *Carditis (clinical or subclinical)*
5. *Sydenham's chorea: this is often a late feature*

Minor criteria:

1. *Raised peak ESR (≥ 30 mm in the first hour) and/or raised CRP (≥ 3.0 mg/dL)*
2. *Fever (≥ 38)*
3. *Arthralgia (not if arthritis a major criteria)*
4. *Prolonged PR interval after accounting for age variability (unless carditis is a major criterion)*

Diagnosis is based on: evidence of recent streptococcal infection Plus:

- **2 major criteria**
- **1 major with 2 minor criteria**

▪ Manifestations:**○ Arthritis:**

- Joint involvement is the most common manifestation of rheumatic fever but the least specific. It is more severe in young adults than in teenagers and children.
- In low-risk population, polyarthritis fulfills the arthritis criteria, where in high-risk population, either polyarthralgia or monoarthritis and/or polyarthritis can be considered.

(1) Low-risk communities are defined as having an ARF incidence of less than 2 per 100,000 school-aged children (usually 5 to 14 years) per year, or an all-age prevalence of RHD of 1 or more per 1000 population per year.

- The joint pain is typically described as *migratory, asymmetric, transient and involving large joints* (e.g the knees, ankles, elbows, wrists and shoulders). It usually affects the *lower limbs initially* before spreading to the upper limbs.
- The arthritis of rheumatic fever responds promptly to NSAIDs within 48 hrs.
- The affected joint may be inflamed for only a few days to 1 week before the inflammation subsides. If joint swelling persists after 4 weeks, it becomes necessary to consider other conditions, such as juvenile idiopathic arthritis or SLE.
- Analysis of the synovial fluid has shown the presence of sterile inflammatory fluid. There may be a reduction in complement components C1q, C3, and C4, suggesting their consumption by immune complexes.
- Radiographs may show features of a joint effusion, but no other abnormalities are noted.
- **Jaccoud arthropathy** (or chronic post-rheumatic fever arthropathy) is a rare manifestation of rheumatic fever characterized by deformities of the fingers and toes. There is ulnar deviation of the fingers, especially the fourth and fifth fingers, flexion of the metacarpophalangeal joints, and hyperextension of the proximal interphalangeal joints (i.e., swan neck deformity).
- **Carditis:**
 - Carditis is the most serious manifestation of rheumatic fever because it may lead to chronic RHD with its attendant complications of AF, stroke, heart failure, infective endocarditis, and death.
 - The incidence of carditis in rheumatic fever varies with the age of the patient. It is reported in 90% to 92% of children under age 3 years, in 50% of children aged 3 to 6 years, and in 32% of teenagers age.
 - The clinical diagnosis of carditis is based on the detection of an organic murmur that was not previously present (to indicate endocarditis), presence of a pericardial friction rub or signs of pericardial effusion (to indicate pericarditis), or cardiomegaly or congestive heart failure (to indicate myocarditis). *Myocarditis* in the absence of valvulitis is unlikely to be rheumatic in origin (It should be accompanied by an apical systolic or basal diastolic murmur).
 - The most common valvular lesion is mitral regurgitation. Aortic regurgitation is less common. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation.

- In patients with a history of previous RHD, a change in the character of the murmurs or the appearance of a new murmur will indicate the presence of acute rheumatic carditis.
- Cardiac involvement may be asymptomatic. Subclinical valvulitis is detected by echocardiography and defined as “Pathologic MR/AR” seen in at least two views with jet length ≥ 2 cm (≥ 1 cm in AR), Peak velocity ≥ 3 m/s and Pansystolic/pandiatolic jet in at least one envelope.
- **Sydenham Chorea:**
 - Chorea may be the only presenting manifestation of rheumatic fever. It is more common in *females*.
 - The latent period between the episode of pharyngitis and the development of chorea is considerably longer (6 to 8 weeks) than for arthritis and carditis.
 - It usually lasts for 8 to 15 weeks (may last for 1 week to 2 years).
 - Chorea is extrapyramidal disorder characterized by the presence of involuntary, purposeless, jerky movements of the hands, arms, shoulders, feet, legs, face, and trunk associated with hypotonia and weakness. The purposeless movements interfere with voluntary activity and *disappear during sleep*.
 - Motor impersistence may be demonstrated by asking the patient to squeeze the examiner’s hand. This results in repetitive, irregular squeezes called the “**milking sign**.”
 - Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, outbursts of anger or crying, and learning difficulties.
 - When chorea occurs alone, ESR, CRP and streptococcal antibody titers may be normal because of the long latent period and resolution of the original infection.
 - Chorea does not occur simultaneously with arthritis but may coexist with carditis.
- **Subcutaneous Nodules:**
 - The subcutaneous nodules of rheumatic fever resemble the nodules of rheumatoid arthritis. They are usually firm, painless, and freely movable over the subcutaneous tissue measuring 0.5 to 2 cm.

- Nodules are usually seen in children with prolonged active carditis rather than in the early stages of rheumatic fever. They may persist for a few weeks but seldom more than 1 month.
- **Erythema Marginatum:**
 - Erythema marginatum is a less common manifestation of rheumatic fever and occurs on the upper arms or trunk but not the face.
 - The rash is evanescent, pink, and nonpruritic. The rash may also become more prominent after a hot shower.
 - Erythema marginatum is suggestive of coexisting carditis.
- **Investigations:**
 - **Recommended for All Cases:**
 - White blood cell count
 - ESR or CRP: always elevated during the acute phase of rheumatic fever in patients with arthritis and are usually normal in patients with chorea.
 - Throat swab for GAS culture before giving antibiotics.
 - Blood culture, if febrile
 - Antistreptococcal serology: both antistreptolysin O (ASO) and anti-DNase B titers (repeat after 10 to 14 days if first test is not confirmatory)
 - ECG: the most common finding is PR prolongation and sinus tachycardia.
 - Chest radiograph
 - Echocardiogram
 - **Tests for Alternative Diagnoses, Depending on Clinical Features:**
 - Repeated blood cultures with temperature spikes if infective endocarditis is suspected
 - Joint aspirate for possible septic arthritis (microscopy and culture)
 - Copper, ceruloplasmin, antinuclear antibody, and drug screen for choreiform movements
 - Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis

- Peripheral blood smear for sickle cell disease.

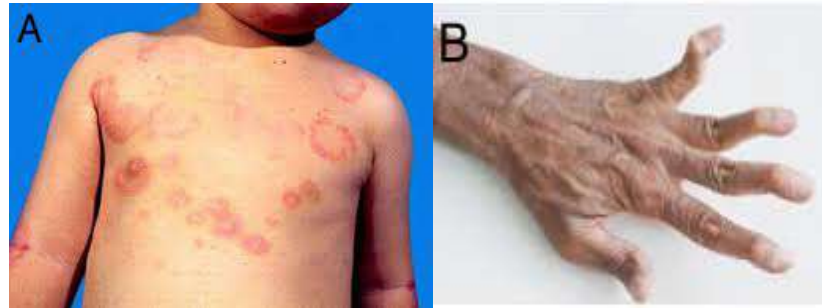


Figure 13-1: (A) Erythema marginatum. (B) Jaccoud arthropathy

Treatment:

The aim of treatment of a proven attack of rheumatic fever is to:

- Suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints.
- Eradicate the GAS from the pharynx.
- Provide symptomatic relief.
- Commence secondary prophylaxis.

Treatment of Acute Rheumatic fever includes:

- **Bed rest** is appropriate mainly to lessen joint pain. The duration of bed rest should be individually determined, but ambulation can usually be started once the fever has subsided and acute-phase reactants are returning to normal. Strenuous exertion should be avoided, especially for those with carditis.
- **IM dose of benzathine benzylpenicillin** (or erythromycin if allergic to penicillin) even if throat swabs taken during the acute attack of rheumatic fever are negative for GAS.

- **Aspirin** (80-100 mg/kg/d in children) has been the preferred treatment for the inflammatory manifestations of RF specifically the arthritis. Aspirin is preferred over steroids as steroids may lead to fluid retention and worsen heart failure symptoms. Neither aspirin nor steroids, despite relieving the symptoms of inflammation, prevent valvular damage.
- If intolerant to aspirin, **Prednisolone** (1-2 mg/kg/day with max. of 60 mg/d) may be used. Gradual tapering is recommended after the clinical and laboratory evidence of disease inactivity.

Prevention:

- **Primary Prevention:** Antibiotic treatment of proven or presumed GAS pharyngitis is effective in reducing the attack rate of rheumatic fever by 70%. The treatment of GAS pharyngitis is directed toward eradication of the bacteria from the upper respiratory tract. The infection can usually be eradicated by a single IM injection of benzathine benzylpenicillin (1.2 million units) or by 10 days' treatment with oral penicillin (Penicillin V 250-500 mg T.D.S).
- **Secondary Prevention:** Recommendations regarding the duration of secondary prophylaxis are based on observational studies. The duration of prophylaxis should be individualized and take into account the socioeconomic conditions and risk of exposure to GAS for that patient.

Table 13-2 Antibiotic regimen for secondary prevention:

| Antibiotic | Dose | Administration |
|---|---|---|
| Benzathine benzylpenicillin ⁽¹⁾ | 1.2 million units (50% if < 30 kg in weight) | <i>Single IM injection every 3-4 weeks</i> ⁽²⁾ |
| Penicillin V | 250 mg B.I.D | <i>Oral</i> |
| Erythromycin | 250 mg B.I.D | <i>Oral</i> |

(1) The evidence from clinical trials is strongly in support of the superiority of IM compared to oral penicillin in the prevention of rheumatic fever recurrences.

(2) The evidence is strong for injections every 2 weeks, with an almost 50% reduction in the risk of rheumatic fever recurrence compared to injections every 4 weeks. The evidence for injections every 3 weeks is less strong. Despite this evidence, WHO recommends intervals of 3 to 4 weeks for the secondary prevention of rheumatic fever.

| | | |
|--------------------|--|-------------|
| Sulfonamide | 1 gm daily (50% if < 30 kg in weight) | <i>Oral</i> |
|--------------------|--|-------------|

Table 13-3: Duration of antibiotic prophylaxis:

| Category of patient | Duration of Prophylaxis |
|--|---|
| Patient without proven carditis | <i>For 5 years after last attack <u>or</u> until 18 years of age (whichever is longer)</i> |
| Patient with carditis (Mild MR or healed carditis) | <i>For 10 years after last attack <u>or</u> until 25 years of age (whichever is longer)</i> |
| More severe valvular disease | <i>Lifelong</i> |
| After valvular surgery | <i>Lifelong</i> |

References and suggested readings:

- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).
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Section

IV

Arrhythmia and Syncope

TO THE POINT

Chapter 14:

General Approach to Tachy-arrhythmias

Action potential:

- **Action potential of atria, ventricles and Purkinje system:** Action potentials are of long duration, especially in Purkinje fibers, where they last 300 msec.
- **Phase 0:** is the **upstroke** of the action potential.
 - Caused by a transient increase in Na^+ conductance which results in an inward Na^+ current that depolarizes the membrane.
 - At the peak of the action potential, the membrane potential approaches the Na^+ equilibrium potential.
- **Phase 1 (Initial repolarization):**
 - Caused by an outward current, in part because of the movement of K^+ ions (favored by both chemical and electrical gradients) out of the cell and in part because of a decrease in Na^+ conductance.
- **Phase 2 (Plateau):**
 - The plateau is maintained by competition between the outward current carried by K^+ and Cl^- ions and the inward current carried by Ca^{2+} moving through $I_{\text{Ca,L}}$ and Na^+ being exchanged for internal Ca^{2+} by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger operating in forward mode.
 - Several potassium currents are activated during the plateau phase, including the rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier currents ⁽¹⁾.
 - During phase 2, outward and inward currents are approximately equal, so the membrane potential is stable at the plateau level.
- **Phase 3 (Repolarization):**

(1) Mutations in the *KvLQT1* subunit, which in combination with the I_{Ks} ancillary subunit (*KCNE1* encoding *minK*) reconstitutes the cardiac I_{Ks} current, are associated with abnormally prolonged ventricular repolarization (LQTS type 1).

- During phase 3, Ca^{2+} conductance decreases, and K^{+} conductance increases including I_{Ks} and I_{Kr} and the inwardly rectifying K^{+} currents I_{K1} and I_{KACh} , which all cause an increase in the movement of positive charges out of the cell. The net membrane current becomes more outward, and the membrane potential moves to the resting potential ⁽¹⁾.

- **Phase 4 (Resting membrane potential):**

- I_{K1} is the current responsible for maintaining the resting potential near the K^{+} equilibrium potential and shuts off during depolarization.

The depolarization of one cell causes the sodium channels of adjacent cells to open and depolarize. There are two properties of electrical propagation:

(1) Conduction velocity, which depends on phase 0;

(2) Refractory period, which depends on the duration of phases 2-3.

A reduction in the steepness of phase 0 (e.g., class I AAD) leads to slower velocity and wide QRS, while a prolonged phase 3 (e.g., class III AAD) leads to a prolonged QT interval.

- **Action potential of the SA and AV nodes:**

- **Phase 4 (spontaneous depolarization):** It accounts for automaticity of SA node cells to generate an action potential spontaneously without neural input. At the end of repolarization, when the membrane potential is very negative (about -60 mV), ion channels (called hyperpolarization-activated cyclic nucleotide-gated [HCN] channels) open that conduct slow, inward

(1) *Loss-of-function mutations in the KCNH2 gene, which encodes the pore-forming subunit of I_{Kr} , prolong phase 3 repolarization, thereby predisposing to the development of torsades de pointes.*

Macrolide antibiotics, several neurologically active agents, and antifungal drugs such as ketoconazole inhibit I_{Kr} and have been implicated in acquired forms of LQTS.

Similarly, mutations in KVLQT1, which encodes the pore-forming subunit of I_{Ks} , will prolong repolarization and predispose to lethal ventricular arrhythmias.

(depolarizing) Na^+ currents. These currents are called "**funny**" currents and abbreviated as " I_f ". These depolarizing currents cause the membrane potential to begin to spontaneously depolarize, initiating Phase 4. As the membrane potential reaches about -50 mV, another type of channel opens, which increases calcium conductance (Transient or T-type Ca^{++} channel). As Ca^{++} enters the cell, the inward directed Ca^{++} currents further depolarize the cell. When the membrane depolarizes to about -40 mV, a second type of Ca^{++} channel opens, (Long-lasting , L-type Ca^{++} channels). Opening of these channels causes more Ca^{++} to enter the cell and to further depolarize the cell until an action potential threshold is reached (usually between -40 and -30 mV).

- **Phase 0**, upstroke is characterized by Ca^{++} rather than Na^+ entry through the L-type Ca^{++} channels ⁽¹⁾. It is slower than phase 0 of the atrial and ventricular cells, thus explaining the slower conduction through the AV node.
- **Phase 3 (Repolarization)** occurs as K^+ channels open, which increases outward directed, hyperpolarizing K^+ currents. Concurrently, L-type Ca^{++} channels become inactivated and close, which decreases the inward depolarizing Ca^{++} currents.

N.B:

- It should be noted that a hyperpolarized state is necessary for pacemaker channels to become activated. Without the membrane voltage becoming very negative at the end of phase 3, pacemaker channels remain inactivated, which suppresses pacemaker currents and decreases the slope of phase 4. This is one reason cellular hypoxia, which depolarizes the cell and alters phase 3 hyperpolarization, leads to a reduction in pacemaker rate (i.e., produces bradycardia).
- Spontaneous phase 4 depolarization may be seen in ischemic atrial or ventricular cells (increased automaticity).

(1) It explains the effect of CCBs on slowing the SA and AV node.

Mechanisms of Arrhythmias:

An arrhythmia may result from the following mechanisms:

1. Reentry (the most common mechanism):

In order to have reentry, adjacent myocardial areas (A and B) need to have different refractory periods and different conduction velocities, separated by an anatomical or functional barrier.

The larger the difference in refractory period between A and B, the easier it is to initiate an arrhythmia; this difference between refractory periods is called the *tachycardia zone*.

The slower the conduction velocity in A, the more likely it is to sustain the arrhythmia (slow conduction leads to a large *excitable gap*).

These areas of slow conduction and different refractory period are seen around a scar (prior infarct, fibrosis, cardiomyopathy), an ischemic area, or a functionally slow area (crista terminalis for atrial flutter, slow pathway of AVNRT) or fast area (accessory pathway of AVRT).

Scarred myocardium is an anatomic barrier for reentry. The peri-scar myocardium has a slow conduction, but shorter action potential and shorter repolarization than the surrounding tissue. An area is functionally slow when fibers in that area are organized transversally rather than longitudinally; electrical activity spreads more slowly transversally than longitudinally through gap junctions.

2. Increased automaticity:

- In this case, atrial or ventricular myocardial cells develop abnormal pacing capacity with spontaneous diastolic depolarization (e.g., accelerated idioventricular rhythm).
- Alternatively, after a pause, latent pacemaker may start firing in phase 4 (e.g., ventricular escape rhythm).
- Like sinus tachycardia, which is an automatic rhythm, an automatic arrhythmia generally displays a warm-up phenomenon at onset and warm-down phenomenon at offset.

3. Triggered activity secondary to afterdepolarizations:

Afterdepolarizations are depolarizing oscillations in membrane potential that occur during the late part of phase 3 repolarization (early afterdepolarization, EAD) or phase 4 (delayed afterdepolarization, DAD).

If the afterdepolarization reaches a threshold potential, arrhythmia may be initiated.

Afterdepolarization, whether EAD or DAD, is related to excessive intracellular accumulation of calcium. **EADs** are mainly seen during a very prolonged repolarization that allows spontaneous calcium release from the sarcoplasmic reticulum (e.g., after a pause or bradycardia). EAD-triggered activity may be due to a congenital or acquired long QT syndrome, electrolyte disturbances, or antiarrhythmic drugs.

DADs, on the other hand, are promoted by a fast heart rate rather than a pause; the fast heart rate impedes reuptake of calcium into the sarcoplasmic reticulum, which increases intracytosolic calcium accumulation and thus the amplitude of DADs. DAD-triggered activity is generally due to ischemia, catecholamine excess, hypoxia, acid-base disorders, or calcium overload from digoxin toxicity. Automaticity may also be due to cavity stretch.

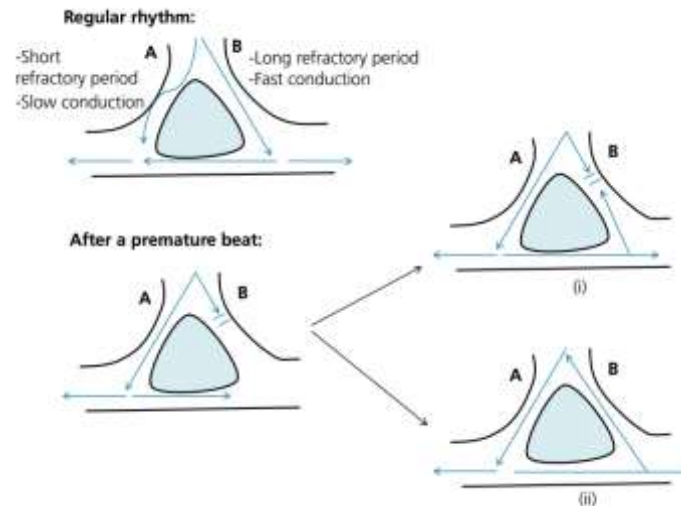


Figure 14-4: Illustration of reentry as a mechanism of tachyarrhythmia. When the rhythm is regular, the electrical activity spreads through both areas simultaneously (*top*). After a **premature beat**, region B is still in its long refractory period, but region A has recovered (*lower left*). The electrical activity spreads through region A, then meets the tail end of region B; at that time, if region B has not recovered from its refractory period, arrhythmia does not occur (i). Since A conducts slowly, region B may well recover from its refractory period, allowing conduction to spread retrogradely through region B (ii). Eventually, this retrograde impulse reaches A faster than the electrical activity originating from the sinus node reaches A. Since A has a short refractory period, the impulse may propagate through A and stimulate the whole cardiac chamber again. Thus, this circle keeps repeating itself, stimulating the myocardial tissue at a rate faster than normal: this is the reentrant tachyarrhythmia. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Table 14-1: Differentiation of various mechanisms of arrhythmias:

| | Reentry | Automaticity | Triggered activity |
|--|---------|--------------|--------------------|
| <i>Induction and termination with pacing</i> | + | - | + |

| | | | |
|---|---|---|-----|
| <i>(=programmed electrical stimulation)</i> | | | |
| <i>Catecholamine facilitation (isoproterenol)</i> | +/- | + | + |
| <i>After entrainment with pacing then interruption of pacing: post-pacing interval=tachycardia cycle length</i> | + if paced from the actual site of reentry (reentry resumes at its own speed) | - | +/- |
| <i>Response to CCBs</i> | | | + |
| <i>Adenosine suppression of atrial arrhythmia</i> | +/- | - | + |

When analyzing a tachycardia, start by looking at three features:

1. Narrow QRS vs. wide QRS (≥ 120 ms) (choose the lead where QRS is widest)
2. Regular vs. irregular ventricular rate
3. Look for P waves and their relationship with QRS complexes.

P waves are usually seen as notches or deflections that fall over the ST–T segments and have a consistent morphology and timing, i.e., those deflections are regularly placed and can be marched out.

P waves are often best seen in lead II, which is generally parallel to the spread of atrial depolarization; and in the lead where T and QRS are smallest (opening up room to see the scattered P waves).

In wide QRS tachycardia, analyze: (i) AV dissociation, and (ii) Number of P waves compared Number of QRS.

In narrow QRS tachycardia, assess the length of the RP interval.

Table 14-2: Differential diagnosis of narrow and wide QRS tachycardias:

Narrow QRS (120 ms) tachycardias

Regular:

- *Physiological sinus tachycardia*
- *Inappropriate sinus tachycardia*
- *Sinus nodal re-entrant tachycardia*
- *Focal AT*
- *Atrial flutter with fixed AV conduction*
- *AVNRT*
- *JET (or other non-re-entrant variants)*
- *Orthodromic AVRT*
- *Idiopathic VT (especially high septal VT)*

Irregular:

- *AF*
- *Focal AT or atrial flutter with varying AV block*
- *Multifocal AT*

Wide QRS (>120 ms) tachycardias

Regular:

- *VT/flutter*
- *Ventricular paced rhythm*
- *Antidromic AVRT*
- *SVTs with aberration/BBB (pre-existing or rate-dependent during tachycardia)*
- *Atrial or junctional tachycardia with pre-excitation/bystander AP*
- *SVT with QRS widening due to electrolyte disturbance or antiarrhythmic drugs*

Irregular:

- *AF or atrial flutter or focal AT with varying block conducted with aberration*
- *Antidromic AV re-entrant tachycardia due to a nodoventricular/fascicular AP with variable VA conduction*
- *Pre-excited AF*
- *Polymorphic VT*
- *Torsade de pointes*
- *Ventricular fibrillation*

Occasionally, AF with very fast ventricular response may apparently resemble a regular narrow QRS tachycardia.

Approach to Narrow QRS complex tachycardias:

Narrow QRS complexes are due to rapid activation of the ventricles via the His Purkinje system (HPS), which suggests that the origin of the arrhythmia is above or within the His bundle. However, early activation of the His bundle can also occur in high septal VTs, thus resulting in relatively narrow QRS complexes (110:140 ms).

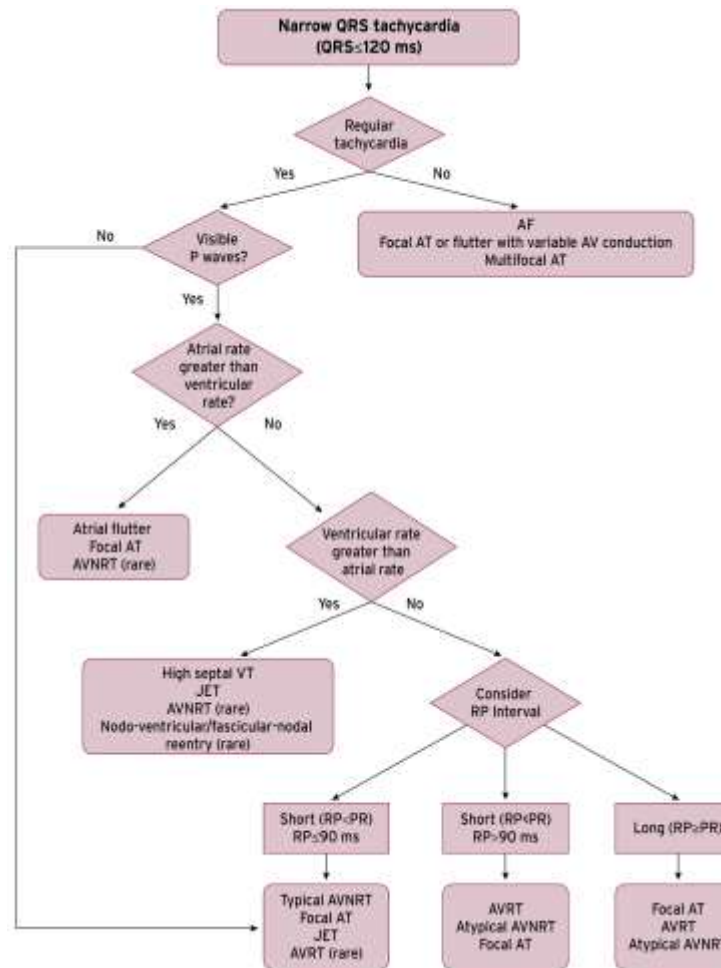


Figure 14-5: Differential diagnosis of narrow QRS tachycardia. Recording of a retrograde P wave should be sought by obtaining a 12 lead Electrocardiogram and, if necessary, using the Lewis leads or even an oesophageal lead connected to a pre-cordial lead (V1) with use of alligator clamps. The 90 ms cut-off is a rather arbitrary number used for surface electrocardiogram measurements if P waves are visible and is based on limited data. In the electrophysiology laboratory, the cut-off of the ventriculoatrial interval is 70 ms. Junctional ectopic tachycardia may also present with atrioventricular dissociation. **Source:** 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

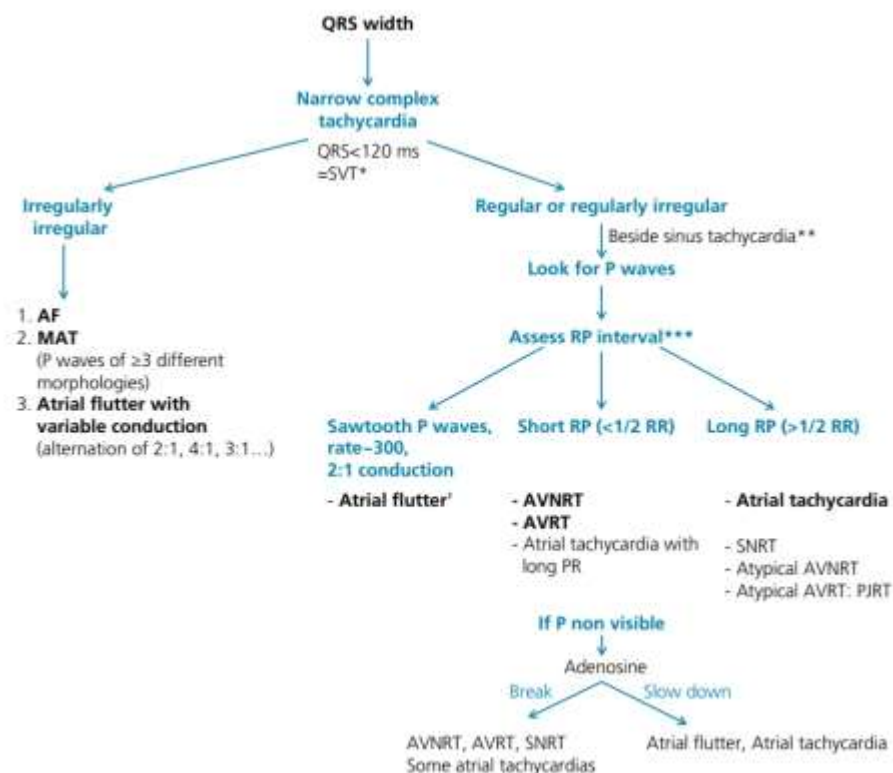


Figure 14-6: Approach to narrow QRS complex tachycardias. *A narrow QRS tachycardia may occasionally be VT. If QRS is relatively narrow (~110–120ms) but different in morphology from the baseline QRS, consider it VT or SVT with aberrancy. **As opposed to other tachycardias, sinus tachycardia has a gradual onset and termination and does not have a fixed rate. *Tachyarrhythmias typically have a sudden onset and offset and a very fixed rate, although they may have a quick warm-up at the beginning.* For example, a tachycardia with a fixed rate of 122bpm on a telemetry monitor suggests arrhythmia. The P wave of atrial tachycardia or SNRT may have a sinus P-wave morphology; the abrupt onset and the steady rate help differentiate these arrhythmias from sinus tachycardia. ***RP interval points to the interval between onset of QRS and onset of the following P wave. The P wave may be a retrograde P wave in AVNRT or AVRT. If this interval is <1/2 of the R–R interval, the tachycardia is a short RP tachycardia. A very short RP interval, i.e. < 90ms, is diagnostic of AVNRT. †Atrial flutter may mimic short RP tachycardia if only the flutter wave following the QRS is seen, or may mimic long RP tachycardia/atrial tachycardia if only the flutter wave preceding the QRS is seen. *Atrial tachycardia with negative P waves preceding the QRS complexes in the inferior leads may, in fact, be atrial flutter.* Look carefully for flutter waves to make the diagnosis. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*.

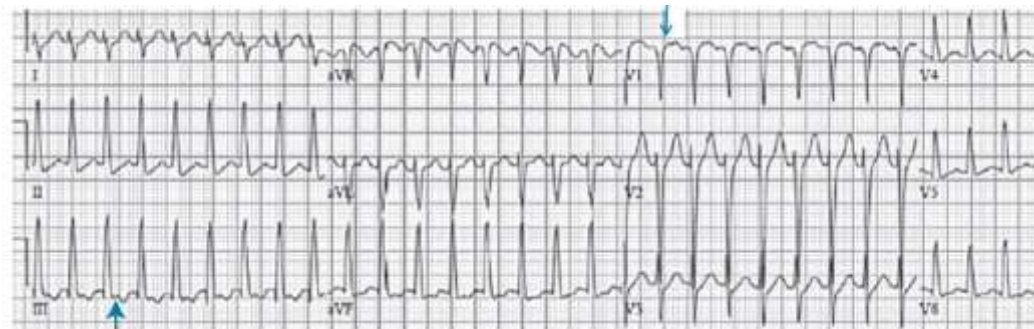


Figure 14-7: Narrow complex tachycardia, regular, rate ~200bpm. Differential diagnosis: AVNRT, AVRT, atrial tachycardia with 1:1 conduction, or atrial flutter with 2:1 conduction.

1. Look for P waves: Ps are seen in leads III, aVF, and V1 (arrows).
2. The RP interval is $< 1/2$ R-R interval, so it is a short RP tachycardia. It is, thus, either AVNRT or AVRT. If RP interval is very short ($< 90\text{ms}$), and if P falls within or immediately past the QRS, looking like pseudo-S in the inferior leads or pseudo-r' in V1, the tachycardia is AVNRT rather than AVRT. On this ECG, RP is $> 90\text{ms}$, and therefore either AVNRT or AVRT is possible. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

N.B:

☞ Recording of a retrograde P wave should be sought by obtaining a 12 lead Electrocardiogram and, if necessary, using the Lewis leads or even an oesophageal lead connected to a pre-cordial lead (V1) with use of alligator clamps. The 90 ms cut-off is a rather arbitrary number used for surface electrocardiogram measurements if P waves are visible and is based on limited data. In the electrophysiology laboratory, the cut-off of the ventriculoatrial interval is 70 ms. Junctional ectopic tachycardia may also present with atrioventricular dissociation.

☞ **Response to adenosine in regular narrow complex tachycardia:**

| Table 14-3: Response to adenosine in regular narrow complex tachycardia: | |
|--|-----------------------------------|
| Response | Diagnosis |
| No effect | - <i>Inadequate dose/delivery</i> |

| | |
|---|--|
| | - <i>High septal VT</i> |
| Gradual slowing then reacceleration | - <i>Sinus tachycardia</i> - <i>Automated focal AT</i> - <i>Junctional ectopic tachycardia</i> |
| Sudden termination | - <i>AVNRT</i> - <i>AVRT</i> - <i>Sinus nodal reentry</i> - <i>Triggered focal AT</i> |
| Persisting atrial tachycardia with transient high grade AV block | - <i>Atrial flutter</i> - <i>Micro-re-entrant focal AT</i> |

Approach to wide QRS complex tachycardias:

Wide QRS tachycardias can be VT, SVT conducting with BBB aberration, or antegrade conduction over an AP, with reported proportions of 80, 15, and 5%, respectively. The correct diagnosis of a VT is critical to management, as misdiagnosis and administration of drugs usually utilized for SVT can be harmful for patients in VT. Therefore, the default diagnosis should be VT until proven otherwise.

A wide complex tachycardia is not necessarily “wide” (≥ 120 ms), as VT or aberrancy originating high in the septum near the His bundle or the bundle branches may be 110–120 ms wide, even narrower than a wide baseline QRS.

▪ **DD of a wide QRS complex tachycardia includes:**

1. **VT:** Approximately 80% of wide complex tachycardias are VTs (95% in case of CAD or HF). Thus, if one is unsure of the diagnosis, it is safer to consider the arrhythmia VT than SVT and treat it as such. However, it is best to look for features characteristic of VT and establish a definitive diagnosis.

2. **SVT (including AF) with aberrancy:** Aberrancy signifies the occurrence of a *functional* RBBB, LBBB, or RBBB+LAFB during a supraventricular tachycardia, leading to a wide complex morphology simulating VT.

SVT with bundle branch block can be due to a *pre-existing* bundle branch block, in which case the QRS morphology during the tachycardia is similar to the QRS morphology during the sinus rhythm, sometimes slightly wider.

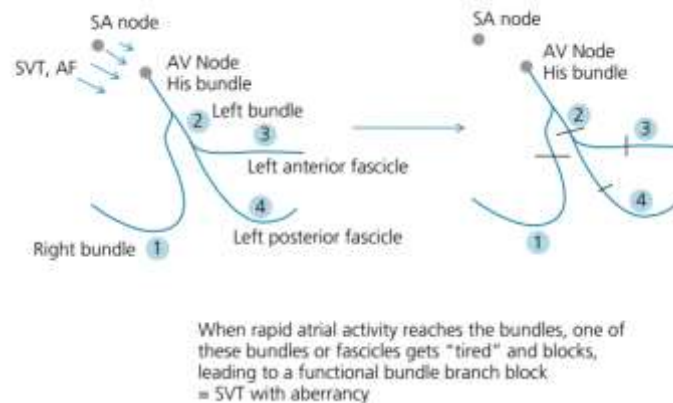
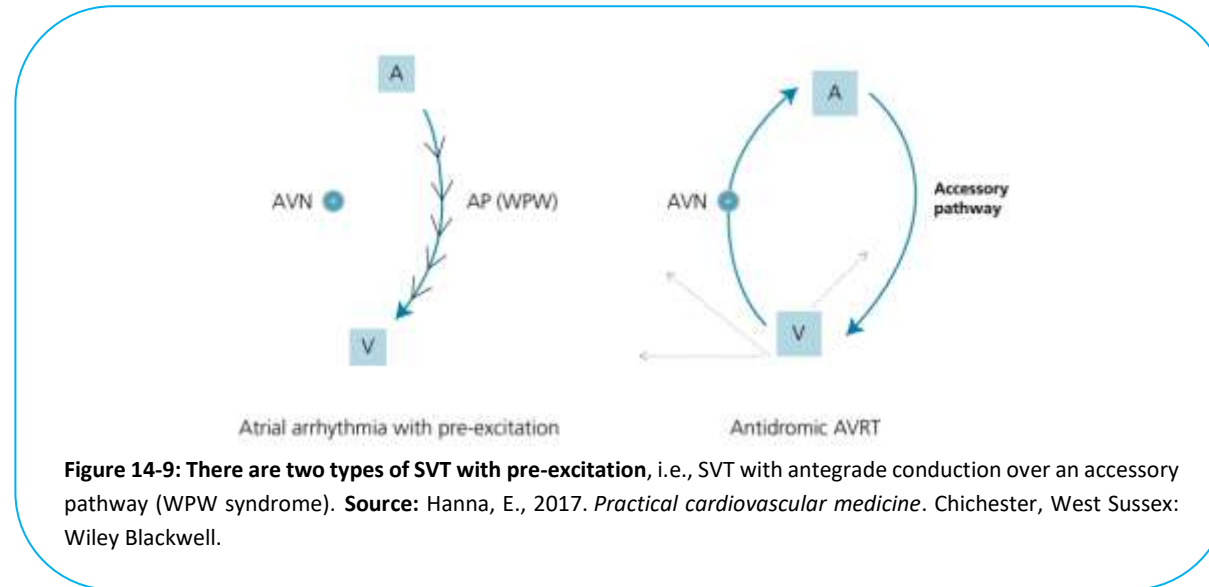


Figure 14-8: Explanation of how a wide QRS complex (aberrancy) may occur with SVT. RBBB, LBBB, or RBBB+LAFB may be seen. RBBB+LPFB is rare. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

3. **SVT (especially AF) with pre-excitation:** This means that the SVT is conducted antegradely over an accessory pathway that connects one atrium to one ventricle, short-circuiting the AV node. There are two types of SVT with pre-excitation:

- **AF or any atrial arrhythmia with pre-excitation.** The atrial waves are preferentially conducted through the fast accessory pathway, leading to a very fast ventricular rate.
- **Antidromic AVRT.** The electrical stimulus spreads down through the accessory pathway then up through the AV node.



4. Other diagnoses:

- Hyperkalemia;
 - Drug toxicity (class I antiarrhythmic agents, tricyclics);
 - Ventricular pacemaker tracking an atrial arrhythmia (lack of mode switch), or
 - Pacemaker- mediated tachycardia.
- **Features characteristic of VT versus SVT with aberrancy:**
 - **Characters of VT:** *Brugada criteria* include the first four features:
 - **AV dissociation** (~100% specific for VT): Two features are characteristic of AV dissociation and imply VT:
 - Cannon A waves on JVP exam that the atria and ventricles contract simultaneously. Irregular cannon A waves imply AV dissociation.

- Variable pulse and variable first heart sound despite a regular rhythm implies AV dissociation. The variable pulse and variable first heart sound make VT mimic AF on exam; however, the monitored rhythm shows a regular rhythm, and this “irregular-sounding regular rhythm” is actually VT.
- QRS morphology inconsistent with a typical RBBB or LBBB.
- Onset of R-to-nadir of S > 100 ms in any precordial lead.
- Monophasic QRS concordance in all precordial leads: Monophasic QRS concordance in the precordial leads signifies that all QRS complexes in V1 through V6 are monophasic and pointing in the same direction, either upward or downward.
- QRS complexes outnumber P waves (with AV association or AV dissociation).
- Deep Q wave in V4–V6, is particularly suggestive of VT.
- A tachycardia that starts with a PVC and has a morphology similar to this PVC is VT.
- In patients with a wide baseline QRS (LBBB or RBBB or non-specific intraventricular conduction delay), **a tachycardia that is wide but narrower than the baseline QRS is VT**
- Right axis deviation: The typical forms of aberrancy, LBBB, RBBB, or RBBB+LAFB, are not associated with a right axis. On the other hand, VT most frequently originates from the ventricle with the largest mass, i.e., LV, and therefore frequently has a right axis.
- **QRS >160ms suggests VT if the baseline QRS is narrow** and in absence of class I antiarrhythmic drug.
- **Presence of capture or fusion complexes.** When an impulse originating from the sinus node conducts down the AV node and captures the ventricles, instead of allowing the VT focus to capture the ventricles, the complex that results is a capture complex squeezed within the VT. If this impulse partially captures the ventricles, while the VT focus partially captures the rest of the ventricles, the resulting complex is a fusion complex.
- **In VT, the QRS complex is wide in its initial portion and has a slow initial upslope or downslope.**
- In aVR, VT is suggested by: (i) dominant, large or wide initial R wave (R or RS complex), or (ii) QR pattern with a slowly downsloping Q wave > 40ms. Normally, aVR consists of a sharp and deep negative deflection, sometimes preceded or followed by a small r wave (QS, rS, or Qr pattern).

- **Characters supportive of SVT:**

- If the patient has a pre-existing RBBB or LBBB, or any intraventricular conduction delay, and the tachycardia has the exact morphology of the baseline QRS, the tachycardia is SVT.
- A tachycardia that starts with a wide aberrant PAC and has a morphology similar to this aberrant PAC is SVT. Also, a tachycardia that is similar in morphology to a previous PVC is VT.
- In SVT with aberration, QRS has a narrow initial deflection that corresponds to the septal depolarization, followed by widening of the terminal QRS portion.

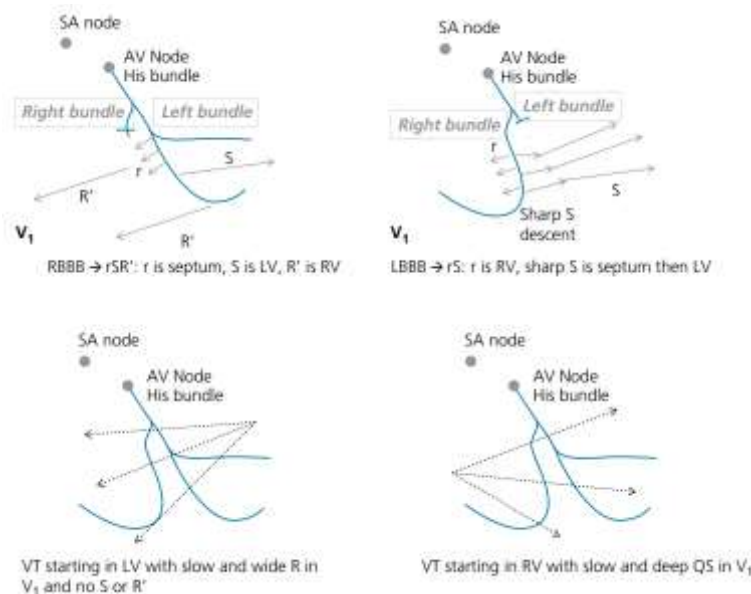


Figure 14-10: Difference in QRS morphology between bundle branch block and VT. The QRS description is in reference to lead V1. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

- **Features characteristic of SVT with pre-excitation:**

Seeing the slurred delta wave on the baseline ECG is diagnostic of pre-excitation; seeing it during tachycardia implies VT or pre-excited SVT.

The most typical SVT with pre-excitation is AF with pre-excitation. In this case, the wide tachycardia is irregular, implying AF rather than VT, with a differential diagnosis that includes AF with aberrancy.

AF with pre-excitation is diagnosed when:

- AF has VT morphological features; **or**
- AF is wide and polymorphic (QRS varies in height and width), bizarre looking, **or**
- AF is very fast (> 200 bpm).

In AF with pre-excitation, the QRS may become wider after a **longer** R–R interval that allows recovery of the accessory pathway's refractory period (as opposed to Ashman's phenomenon present in AF with aberrancy).

| Table 14-4: Summary of key ECG criteria that suggest VT rather than SVT in wide complex tachycardia: | |
|--|--|
| AV dissociation | <i>Ventricular rate > atrial rate</i> |
| Fusion/capture beats | <i>Different QRS morphology from that of tachycardia</i> |
| Chest lead negative concordance | <i>All precordial chest leads negative</i> |
| RS in precordial leads | <i>- Absence of RS in precordial leads - RS >100 ms in any lead ⁽¹⁾</i> |
| QRS complex in aVR | <i>- Initial R wave - Initial R or Q wave > 40 ms - Presence of a notch of a predominantly negative complex</i> |

(1) **RS**: beginning of R to deepest part of S.

| | |
|---|--|
| QRS axis -90 to ± 180 | <i>Both in the presence of RBBB and LBBB morphology</i> |
| R wave peak time in lead II | <i>R wave peak time ≥ 50 ms</i> |
| RBBB morphology | <ul style="list-style-type: none"> - Lead V1: Monophasic R, Rsr', biphasic qR complex, broad R (> 40 ms), and a double-peaked R wave with the left peak taller than the right (the so-called 'rabbit ear' sign) - Lead V6: R:S ratio < 1 (rS, QS patterns) |
| LBBB morphology | <ul style="list-style-type: none"> - Lead V1: Broad R wave, slurred or notched-down stroke of the S wave, and delayed nadir of S wave - Lead V6: Q or QS wave |

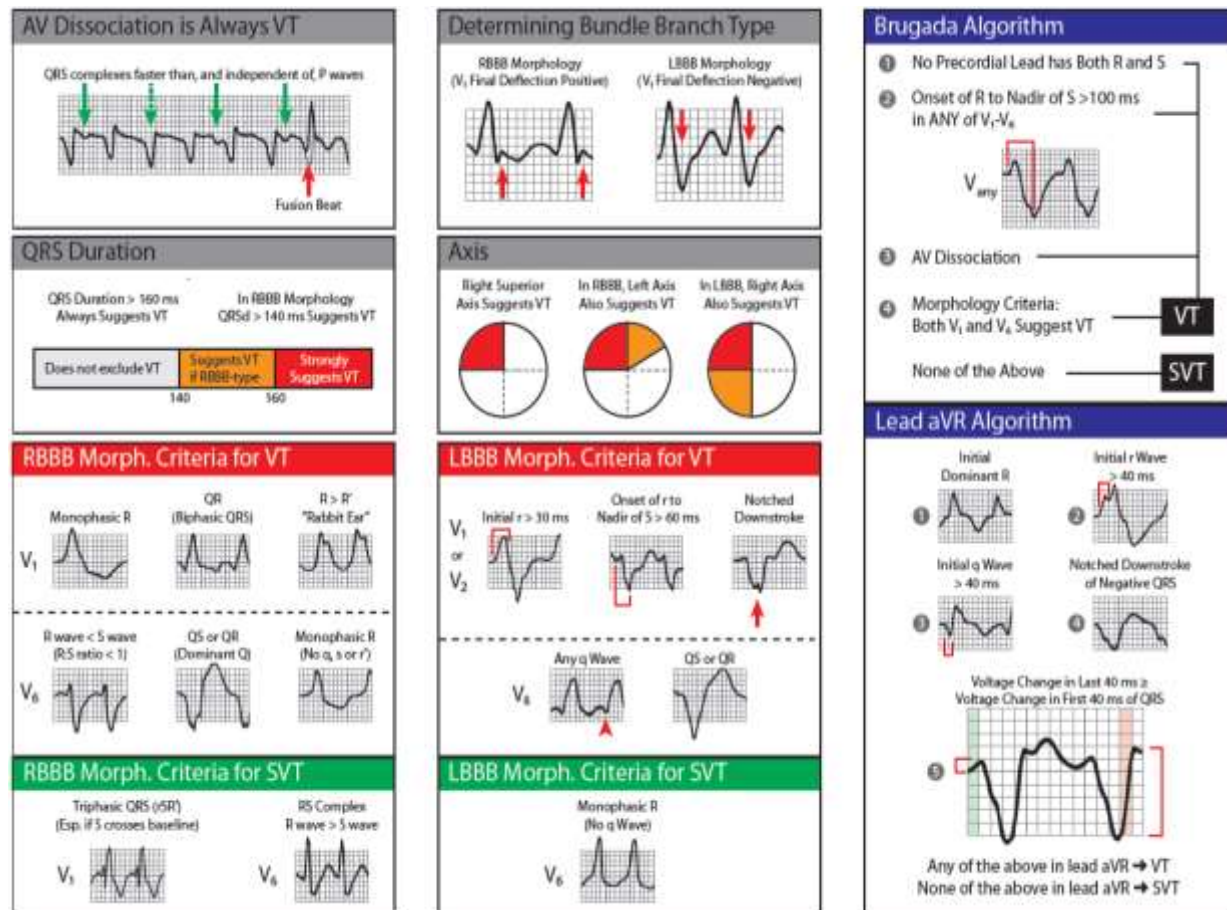


Figure 14-11: Morphological Criteria for Discriminating Ventricular Tachycardia from Supraventricular Tachycardia with Aberration. Source: John B Garner, John M Miller. Wide Complex Tachycardia - Ventricular Tachycardia or Not Ventricular Tachycardia, That Remains the Question. Arrhythmia & Electrophysiology Review 2013;2(1):23-9

Table 14-5: Criteria used for differentiation between VT and SVT in with aberrancy:

| Kindwall Criteria | Wellens criteria | Burgada Criteria | Miller Criteria |
|--|---|--|--|
| Any of the following criteria favors VT: | | | |
| <i>R > 30 msec in V₁ or V₂</i> | <i>AV dissociation</i> | <i>Absence of RS complex in all precordial leads</i> | <i>Initial R wave in aVR</i> |
| <i>Any Q in V₆</i> | <i>QRS width > 140 msec</i> | <i>Longest R/S interval > 100 msec in any precordial lead</i> | <i>aVR with initial r or q > 40 msec</i> |
| <i>>60 msec to S wave nadir in V₁ or V₂</i> | <i>Left axis deviation > -30 degrees</i> | <i>AV dissociation</i> | <i>aVR with a notch on the descending limb of a negative onset and predominantly negative QRS in aVR</i> |
| <i>Notched downstroke S wave in V₁ or V₂</i> | <i>If RBBB morphology, R- to S- ratio < 1</i> <i>If LBBB morphology, S in V₁-V₂</i> | <i>If RBBB morphology,</i> <ul style="list-style-type: none"> ○ <i>monophasic R or qR in V₁</i> ○ <i>R taller than R'</i> ○ <i>rS in V₆</i> <i>If LBBB morphology,</i> <ul style="list-style-type: none"> ○ <i>Initial R > 40 msec</i> ○ <i>Slurred or notched S in V₁ or V₂</i> ○ <i>Beginning of Q or QS in V₆</i> | <i>In aVR, mV of initial 40 msec divided by terminal 40 msec</i> |

Table 14-6: Predictive Values and Accuracies of the Most Common VT Criteria:

| | Original Paper | Later Studies |
|--------------------------------------|----------------------------------|---------------|
| In RBBB and LBBB Morphologies | Positive Predictive Value | |
| AV dissociation → VT | 100% | 100% |

| | | |
|------------------------------------|----------------------------------|---------|
| Precordial concordance → VT | 100% | 89-100% |
| 'Northwest' axis (> 270 °) → VT | - | 95-96% |
| In RBBB Morphology Only | Positive Predictive Value | |
| V1: Rsr' (Left peak > right) → VT | 100% | 100% |
| Left axis deviation → VT | 94% | 88-96% |
| QRS width > 140 → VT | 100% | 89% |
| V1: Mono- or biphasic QRS → VT | 97% | 82-100% |
| V6: R to S ratio < 1 → VT | 90% | 90-100% |
| V1: rSR (S crosses baseline) → SVT | 91% | 93% |
| In LBBB Morphology Only | Positive Predictive Value | |
| QRS duration > 160 ms → VT | 100% | 98-99% |
| Right axis deviation → VT | 100% | 87-96% |
| V6: Any q wave → VT | 100% | 98% |

Acute management in the absence of an established diagnosis:

▪ **Regular Narrow QRS (120 ms) tachycardias:**

Vagal maneuvers can be used to terminate an episode of narrow QRS SVT. The effectiveness of conventional vagal maneuvers in terminating SVT, when correctly performed, has been reported as between 19 and 54%. Vagal maneuvers include different techniques used to stimulate the receptors in the internal carotid arteries. This stimulation causes a reflex stimulation of the vagus nerve, which results in the release of acetylcholine, which may in turn slow the electrical impulse through the AVN and slow the heart rate. The Valsalva maneuver is a safe and internationally recommended first-line emergency treatment for SVT. The Valsalva maneuver has generally been shown to be most effective in adults, and in AVRT rather than AVNRT. A modified approach to the Valsalva maneuver provides a considerable enhancement of conversion success rates. This enhanced method

requires the Valsalva to be completed semi-recumbent, with supine repositioning and passive leg raise after the Valsalva strain. Blowing into a 10 mL syringe with sufficient force to move the plunger may standardize the approach. Carotid sinus massage is performed with the patient's neck in an extended position, with the head turned away from the side to which pressure is applied. It should always be unilateral as there is a potential risk with bilateral pressure, and it should be limited to 5 s. The patient should be monitored. This technique should be avoided in patients with previous transient ischemic attack or stroke, and in patients with carotid bruits.

Table 14-7: ESC Recommendations for the acute management of narrow QRS tachycardia in the absence of an established diagnosis:

| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Hemodynamically unstable patients | | |
| <i>Synchronized DC cardioversion is recommended for hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients | | |
| <i>A 12 lead ECG during tachycardia is recommended.</i> | I | C |
| <i>Vagal maneuvers, preferably in the supine position with leg elevation, are recommended.</i> | I | B |
| <i>Adenosine (6-18 mg i.v. bolus) is recommended if vagal maneuvers fail.</i> | I | B |
| <i>Verapamil or diltiazem (i.v.) should be considered, if vagal maneuvers and adenosine fail.</i> | IIa | B |
| <i>Beta-blockers (i.v. esmolol or metoprolol) should be considered if vagal maneuvers and adenosine fail.</i> | IIa | C |
| <i>Synchronized direct-current cardioversion is recommended when drug therapy fails to convert or control the tachycardia.</i> | I | B |

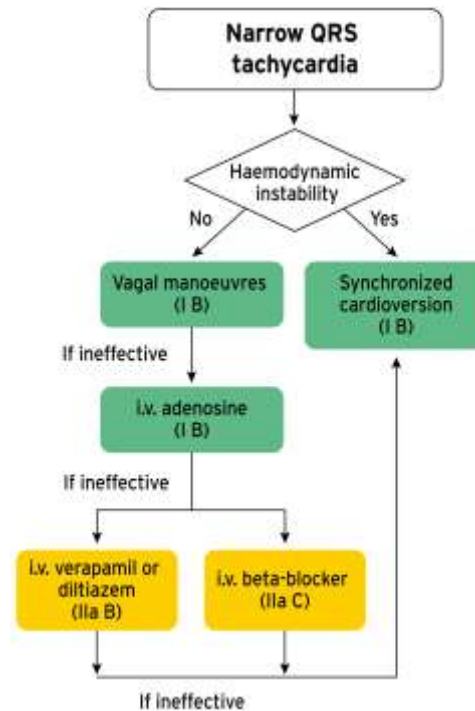


Figure 14-12: Acute therapy of narrow QRS tachycardia in the absence of an established diagnosis. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

N.B:

In a hemodynamically unstable patient with supraventricular tachyarrhythmia (shock or severe HF), always ask yourself: did the tachyarrhythmia cause the shock **or** did the shock cause an increase in heart rate with a secondary SVT or AF?

Typically, to attribute a shock to SVT or AF, the heart rate must be > 150 bpm. In addition, clinical features suggestive of another primary process should be sought (sepsis, acute bleed/severe anemia, tamponade, massive PE); in these cases, tachycardia is not the isolated cause of the instability, it is rather the consequence.

For example, in a patient with BP 75/50 mmHg and AF rate of 125 bpm, AF is likely secondary to the shock rather the cause of the shock. If a tachyarrhythmia faster than 150 bpm is assumed to be the cause of instability, emergent DC cardioversion should be performed.

▪ **Regular Wide QRS (>120 ms) tachycardias:**

| Table 14-8: ESC Recommendations for the acute management of wide QRS tachycardia in the absence of an established diagnosis: | | |
|--|-------|-------|
| Recommendation | Class | Level |
| Hemodynamically unstable patients: | | |
| <i>Synchronized DC cardioversion is recommended in hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients | | |
| <i>A 12 lead ECG during tachycardia is recommended.</i> | I | C |
| <i>Vagal maneuvers are recommended.</i> | I | C |
| <i>Adenosine should be considered if vagal maneuvers fail and there is no pre-excitation on a resting ECG.</i> | IIa | C |
| <i>Procainamide (i.v.) should be considered if vagal maneuvers and adenosine fail.</i> | IIa | B |
| <i>Amiodarone (i.v.) may be considered if vagal maneuvers and adenosine fail.</i> | IIb | B |
| <i>Synchronized DC cardioversion is recommended if drug therapy fails to convert or control the tachycardia.</i> | I | B |
| <i>Verapamil is not recommended in wide QRS complex tachycardia of unknown aetiology.</i> | III | B |

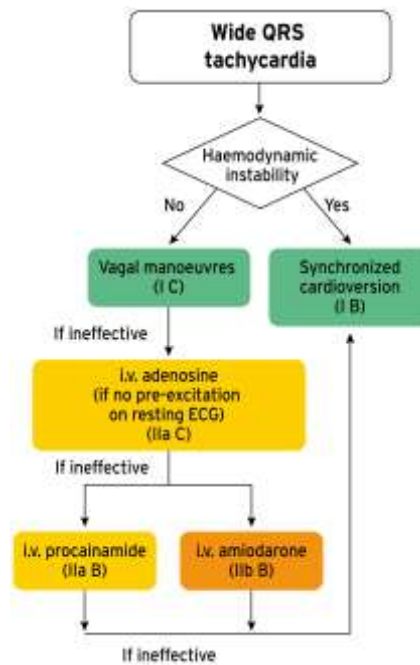


Figure 14-13: Acute therapy of wide complex tachycardia in the absence of an established diagnosis. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

- **Irregular tachycardias:**

A wide QRS irregular tachycardia is usually a manifestation of AF. Rarely, polymorphic VT and, very rarely, monomorphic VT may also present as irregular tachycardias. Electrical cardioversion is the acute treatment of choice in irregular pre-excited tachycardias associated with hemodynamic instability.

If the rhythm is well tolerated with a narrow QRS-complex irregular tachycardia, this should be considered likely to be AF, and rate control with beta-blockers or calcium channel blockers, and elective chemical or electrical cardioversion once thromboprophylaxis is in place, may be appropriate.

Chapter 15:

Supraventricular Tachycardia

Classification:

The term 'SVT' literally indicates tachycardia [atrial rates > 100 b.p.m. at rest], the mechanism of which involves tissue from the His bundle or above. Traditionally, SVT has been used to describe all kinds of tachycardias apart from ventricular tachycardias (VTs) and AF. It has therefore included tachycardias such as atrioventricular (AV) re-entry due to accessory connections, which is not, in essence, a supraventricular rhythm.

Table 15-1: Conventional classification of supraventricular tachycardias:

Atrial tachycardias:

(1) Sinus tachycardia:

- *Physiological sinus tachycardia*
- *Inappropriate sinus tachycardia*



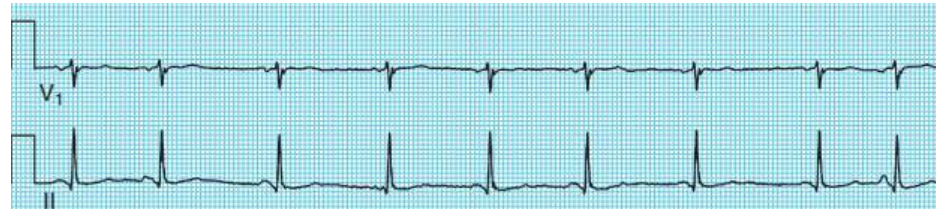
- *Sinus nodal re-entrant tachycardia (SANRT): focal atrial tachycardia due to micro-reentry circuits arising from the sinus node. ECG features of SANRT include: P wave morphology similar to that seen in sinus tachycardia, frequent premature atrial complexes (PACs) toward the beginning or end of the tachycardia, abrupt onset and termination, and heart rate that is usually between 100 to 150 beats per minute.*



(2) Focal AT: *form of supraventricular tachycardia originating from a single ectopic focus within the atria but outside of the sinus node. It is characterized by consistent, abnormal P wave morphology and axis (e.g. inverted in inferior leads) indicating an ectopic focus.*



(3) Multifocal (Chaotic) AT: *A rapid, irregular atrial rhythm arising from multiple ectopic foci within the atria with varying PP, PR and RR intervals. MAT shows at least 3 distinct P-wave morphologies in the same lead. It is most commonly seen in patients with severe COPD or congestive heart failure. It is typically a transitional rhythm between frequent PACs and atrial flutter/fibrillation.*



(4) Atrial flutter Or Macro-reentrant atrial tachycardia (MRAT):

- **Cavotricuspid isthmus⁽¹⁾-dependent MRAT:**

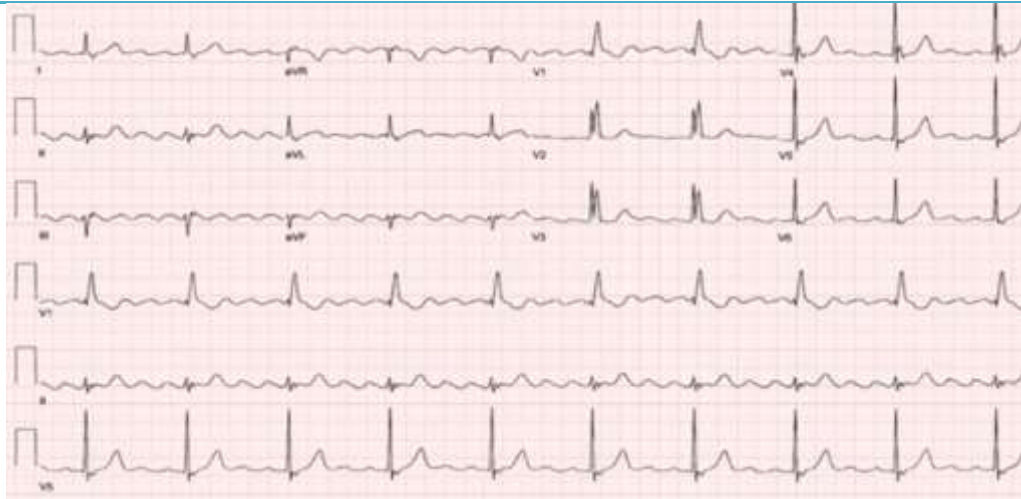
- Typical flutter= counter-clockwise (common) or
- Reverse typical flutter= clockwise.
- Other cavotricuspid isthmus-dependent MRAT

- **Non-cavotricuspid isthmus-dependent MRAT:** reentrant circuits can arise either in RA or LA (e.g around the SVC, pulmonary veins, scars).



Typical atrial flutter. Typical AFL usually represents counterclockwise activation around the RA through the cavotricuspid isthmus. ECG features: sawtooth negative waves in inferior leads and isoelectric segment with positive P waves in V1.

(1) Cavotricuspid isthmus (CTI) is a narrow isthmus bordered by the IVC and crista terminalis posteriorly and the tricuspid annulus anteriorly. The crista terminalis is a fibrous band that separates the anterior and posterior parts of the RA, constitutes the electrical barrier in front of which the Aflutter circuit is sustained.



Reverse typical clockwise atrial flutter. ECG features: Positive waves (often notched, usually not sawtooth) in inferior leads, and broad negative P waves in V1 consistent with reentry around the cavotricuspid isthmus in a clockwise direction.

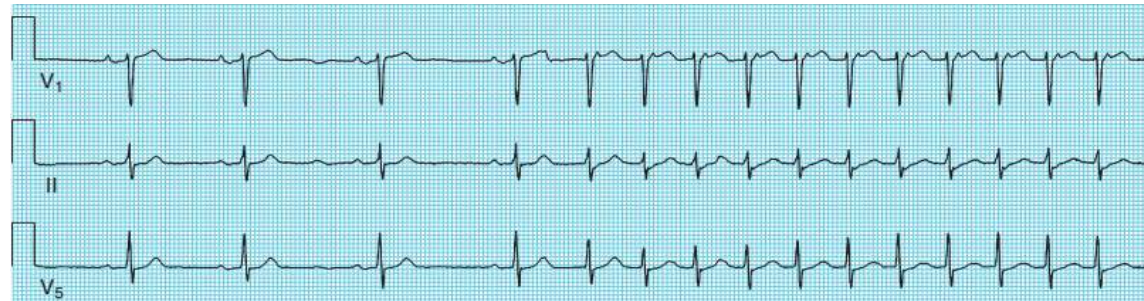


Atypical atrial flutter. ECG shows rapid atrial activity without typical inferior sawtooth waves suggesting CTI-independent flutter. Negative Flutter waves in V1 suggests a right atrial circuit.

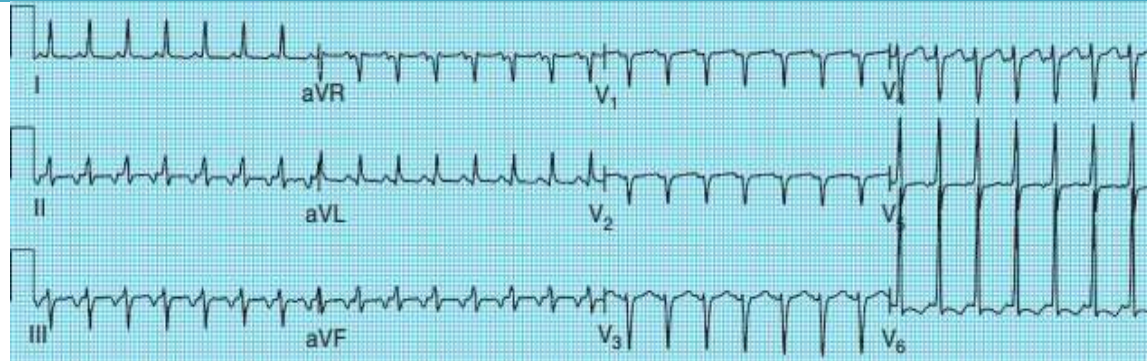
AV junctional tachycardias:

(1) Atrioventricular nodal re-entrant tachycardia (AVNRT): AVNRT is caused by a reentry circuit in or around the AV node. The circuit is formed by the creation of two pathways forming the re-entrant circuit, namely the slow and fast pathways.

- **Typical (Slow-Fast AVNRT):** Associated with Slow AV nodal pathway for antegrade conduction and Fast AV nodal pathway for retrograde conduction. The retrograde P wave is obscured in the corresponding QRS or occurs at the end of the QRS complex as pseudo r' (in V1) **or** S waves (in II, III, aVF).
- **Atypical (Fast-Slow AVNRT):** Associated with Fast AV nodal pathway for antegrade conduction and Slow AV nodal pathway for retrograde conduction. The retrograde P wave appears after the corresponding QRS.



Atrioventricular nodal reentry tachycardia. This lead V1, II, and V5 rhythm strip shows a narrow QRS tachycardia that is AVNRT with antegrade conduction down the slow pathway and retrograde activation up the fast pathway of the AV node (AVN). The tracing begins with four beats of sinus rhythm. A premature atrial complex (seen deforming the T wave of the fourth complex) is conducted to the ventricle with a long PR interval (reflecting conduction down the slow AVN pathway). This is followed by a regular narrow QRS complex tachycardia. After the first beat of the SVT, retrograde P waves are best seen in V1 as small R'-like deflections at the end of the QRS complexes. This demonstrates the very short RP interval (< 90ms) consistent with AVNRT and helps to distinguish AVNRT from other short RP tachycardias with a longer RP interval (> 100ms), such as AV reentrant tachycardia with an accessory pathway that conducts in the retrograde direction.



Atypical atrioventricular nodal reentry tachycardia. This 12-lead ECG shows a long RP narrow complex tachycardia that represents atypical AVNRT (diagnosis made at EP study). Activation proceeds antegrade down the fast pathway of the AV node and then retrograde up the slow pathway, resulting in the long RP interval. The differential diagnosis for a long RP tachycardia includes AT and AV reentry tachycardia mediated by a concealed slowly conducting, decremental retrograde accessory pathway.

(2) Non-re-entrant junctional tachycardia:

- JET (*junctional ectopic or focal junctional tachycardia*)
- *Other non-re-entrant variants*

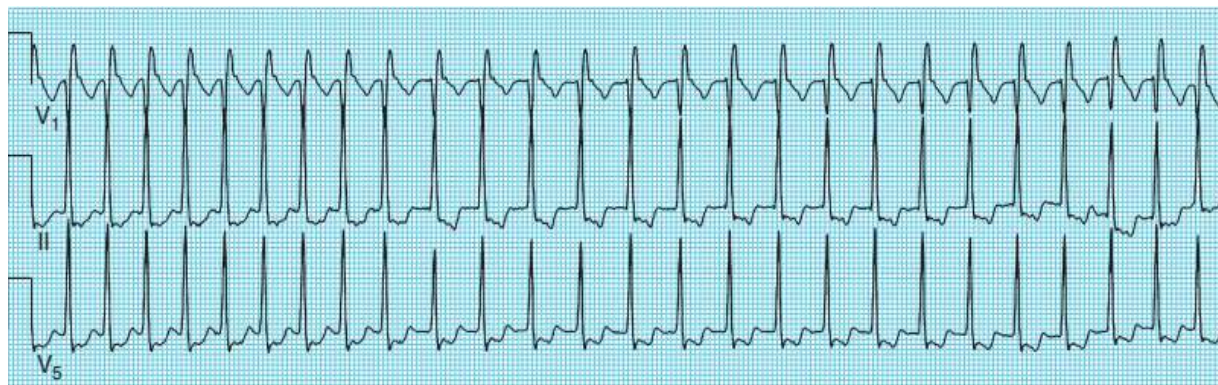


This lead V1 and II rhythm strip shows a rapid (rate approximately 107bpm) junctional rhythm that is characterized by retrograde P waves or the absence of P waves. These findings are consistent with a JT.

Atrioventricular re-entrant tachycardia (AVRT):

AVRT is a form of paroxysmal supraventricular tachycardia. A reentry circuit is formed between the normal conduction system and the accessory pathway resulting in circus movement.

- **Orthodromic (including PJRT):** anterograde conduction occurs via the AV node, with retrograde conduction occurring via the accessory pathway. This can occur in patients with a concealed pathway. It is characterized by:
 - Rate usually 200-300 bpm
 - P waves may be buried in QRS complex or retrograde
 - QRS < 120 ms unless pre-existing bundle branch block, or rate-related aberrant conduction
 - QRS alternans: phasic variation in QRS amplitude associated with AVNRT and AVRT, (distinguished from electrical alternans by a normal QRS amplitude).
- **Antidromic:** anterograde conduction occurs via the accessory pathway with retrograde conduction via the AV node. Much less common than orthodromic AVRT, occurring in ~5% of patients with WPW. It is characterized by:
 - Rate usually 200-300 bpm
 - Wide QRS complexes due to abnormal ventricular depolarisation via accessory pathway



Atrioventricular reentrant tachycardia. This lead V1, II, and V5 rhythm strip shows a short RP narrow QRS complex tachycardia with an RP exceeding 100ms, consistent with AV reentry tachycardia. The QRS complexes show a typical RBBB morphology. The retrograde limb of the reentry circuit is the accessory pathway. In this case the patient's baseline ECG shows sinus rhythm with no evidence of the delta wave of WPW syndrome conduction, suggesting a "concealed" bypass tract that can conduct only in a retrograde direction.



Permanent junctional reciprocating tachycardia. This 12-lead ECG shows a regular narrow complex SVT with a long RP interval, the differential for which includes atrial tachycardia, atypical AV node reentrant tachycardia, and PJRT. The negative P waves in the inferior leads indicate the atria are being activated in a low-to-high direction. This patient was shown to have PJRT at the time of an EP study. PJRT is a misnomer; it is not a junctional reciprocating tachycardia, but rather it is an orthodromic SVT that involves a septal bypass tract that, unlike other bypass tracts, has decremental conduction with prolonged ventricle to atrium (V-A) conduction.

Evaluation:

Table 15-2: Initial evaluation of the patient with supraventricular tachycardia:

Standard:

- History, physical examination, and 12 lead ECG
- Full blood counts, biochemistry profile, and thyroid function
- An ECG during tachycardia should be sought.
- Transthoracic echocardiography

Optional:

- *Exercise tolerance testing*
- *24 h ECG monitoring, transtelephonic monitoring, or an implantable loop recorder*
- *Myocardial ischaemia testing in patients with risk factors for CAD (including men aged > 40 years and post-menopausal women).*
- *An EPS should be considered for a definitive diagnosis and when catheter ablation is anticipated.*

Sinus tachycardia:

Sinus tachycardia is defined as a sinus rate > 100 b.p.m. On the ECG, the P wave is positive in leads I, II, and aVF, and biphasic/negative in lead V1. Sinus tachycardia is not a primary rhythm abnormality. It is secondary to cardiac, pulmonary, septic, or metabolic issues. Thus, sinus tachycardia is not typically treated with rate-controlling agents. The underlying cause is targeted.

Table 15-3: Causes of physiological sinus tachycardia:

| | |
|-----------------------------|---|
| Physiological causes | <i>Emotion, physical exercise, sexual intercourse, pain, pregnancy</i> |
| Pathological causes | <i>Anxiety, panic attack, anaemia, fever, dehydration, infection, malignancies, hyperthyroidism, hypoglycaemia, pheochromocytoma, Cushing's disease, diabetes mellitus with evidence of autonomic dysfunction, pulmonary embolus, myocardial infarction, pericarditis, valve disease, congestive heart failure, shock</i> |
| Drugs | <i>Epinephrine, norepinephrine, dopamine, dobutamine, atropine, beta-2 adrenergic receptor agonists (salbutamol), methylxanthines, doxorubicin, daunorubicin, beta-blocker withdrawal</i> |
| Illicit drugs | <i>Amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy, crack, cocaine</i> |
| Other | <i>Caffeine, alcohol</i> |

Table 15-4: ESC Recommendations for the therapy of sinus tachycardias:

| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| Inappropriate sinus tachycardia (IST): | | |
| <p>IST is a non-paroxysmal sinus tachycardia that is present most of the day, at rest and/or mild physical effort, out of proportion to any physiologic need. The mean 24-hour sinus rate on Holter is often > 90 bpm. IST is due to a dysautonomia that activates the sinus node's I_f current and is mainly seen in young women (< 50 years of age). IST is associated with symptoms of palpitations, fatigue, dizziness, and orthostatic intolerance. In fact, the use of ivabradine eliminated > 70% of IST symptoms in one study. β-blockers and CCBs may also be effective, but may not be well tolerated in dysautonomic patients. Sinus node ablation is only temporarily effective, as tachycardia may arise from other sinus sites after ablation, the main issue being autonomic dysfunction.</p> | | |
| <i>Evaluation and treatment of reversible causes is recommended.</i> | I | C |
| <i>Ivabradine alone or in combination with a beta-blocker should be considered in symptomatic patients.</i> | IIa | B |
| <i>Beta-blockers should be considered in symptomatic patients.</i> | IIa | C |
| Sinus nodal re-entrant tachycardia: | | |
| <i>Non-dihydropyridine calcium channel blockers (verapamil or diltiazem) in the absence of HFrEF, may be considered in symptomatic patients.</i> | IIb | C |
| <i>Catheter ablation should be considered in symptomatic patients who do not respond to drug therapy.</i> | IIa | C |
| Postural orthostatic tachycardia syndrome (POTS): | | |
| <p>POTS is defined as an increase in HR \geq 30 bpm within 10 min of standing, without orthostatic hypotension in addition to an early increase in rate during exercise; it is sometimes associated with IST.</p> <p>POTS is a form of cardiovascular deconditioning that starts after a period of bedrest (e.g., surgery, acute illness), sometimes in hospitalized patients. This deconditioning leads to reduced stroke volume, reduced renin-angiotensin activation (low blood volume), and peripheral autonomic denervation with lack of vasoconstriction. As such, sinus</p> | | |

tachycardia is often useful in POTS because it maintains BP and compensates for the low stroke volume and vascular tone.

A regular and progressive exercise programme should be considered.

IIa B

The consumption of $\leq 2-3$ L of water and 10-12 g of sodium chloride daily may be considered.

IIb C

Midodrine, low-dose non-selective beta blocker⁽¹⁾, or pyridostigmine may be considered.

IIb B

Ivabradine may be considered.

IIb C

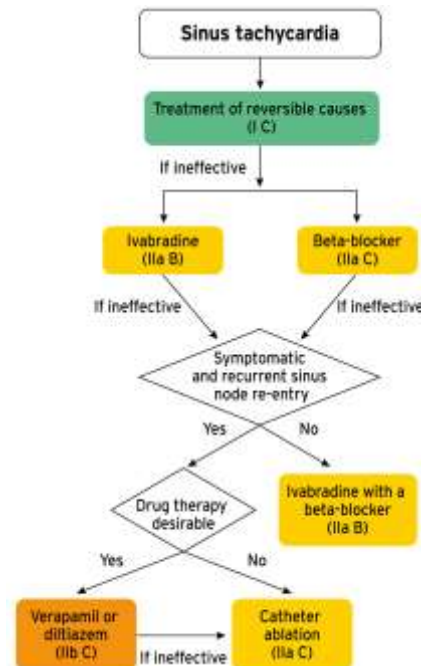


Figure 15-1: Therapy of sinus tachycardias. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

(1) Through reducing cardiac baroreceptor activation, lowering blood norepinephrine level, and inhibiting sympathetic nerve activity.

Focal atrial tachycardia:

Focal Atrial tachycardia (AT) is defined as an organized atrial rhythm ≥ 100 b.p.m. initiated from a discrete origin and spreading over both atria in a centrifugal pattern. The ventricular rate varies, depending on AV nodal conduction.

- **Electrophysiological mechanisms:** Atrial tachycardia (AT) may be initiated by three different mechanisms: microreentry, automaticity, and triggered activity.

- The automatic mechanism is rare in older patients. *The relative frequency of the reentry increases and automaticity decreases beyond the age of 65. Automatic AT and triggered-activity AT are mostly seen in patients < 60–70 years of age who often do not have structural heart disease.*

- Approximately 40% of patients with sustained AT have an underlying CV disease, particularly in the case of reentrant AT. In fact, reentrant AT in older patients is frequently associated with AF or Aflutter.

- AT, particularly automatic AT, may be related to acute illness or metabolic disorders (hypoxia, sepsis).

- Reentry and triggered activity can be induced and terminated with programmed electrical stimulation. On the other hand, automatic AT cannot be initiated or terminated with pacing or premature stimuli ⁽¹⁾.

- **Site of origin:**

- AT most commonly originates from the **RA** (82%). It typically arises around the tricuspid annulus, the crista terminalis (most common two sites, ~35% each).

- It may also arise around prior scars (e.g., pulmonary vein isolation for AF).

- Approximately 10% of patients have multiple foci, particularly older patients or those with underlying structural heart disease, where the prevalence of multiple foci increases to ~25%.

(1) The surface ECG may help differentiate automaticity from reentry:

- In reentry, the PAC that initiates the arrhythmia may have a different P-wave morphology than the arrhythmia.

- In automaticity, the P wave that initiates the arrhythmia has a similar morphology to the P wave of the arrhythmia.

▪ **Natural history:**

AT may be seen at any age, the mean being 40 years old. Up to 65% of patients have spontaneous remission of AT with time, and a lack of recurrence with cessation of antiarrhythmic therapy. This is more common with automatic AT of young patients, especially those < 25 years of age.

▪ **ECG:**

- Regular P wave rate, 100-240 per minute (< atrial rate of Aflutter, 200–340 per minute).
- Isoelectric baseline is seen between P waves (different from typical Aflutter).
- Atrioventricular conduction is usually 1:1. *A conduction block (2:1) suggests digoxin toxicity or hypokalemia.*
- PR interval is normal or prolonged, RP interval is long (> half R–R interval). Thus, AT is usually a long RP tachycardia (as opposed to typical AVNRT and AVRT, which are short RP tachycardias).
- **Localization of the atrial origin of AT:** look at the morphology in leads V1, I-aVL, and II-III-aVF to:
 - Negative P wave in leads II, III, and aVF implies a **low atrial origin** that simulates a retrograde P wave ⁽¹⁾; a positive P wave in leads II, III, and aVF implies a **high atrial origin**.
 - P wave that is positive in V1 and negative in the left lateral leads I and aVL is typical of a **left atrial origin**, with the exception of a right superior pulmonary vein origin (the latter simulates RA origin).

(1) *An atrial tachycardia with a low atrial origin resembles PJRT (incessant slow AVRT). In both cases, the P wave is retrograde-like, i.e., negative in leads II/III/aVF, and the RP interval is long.*

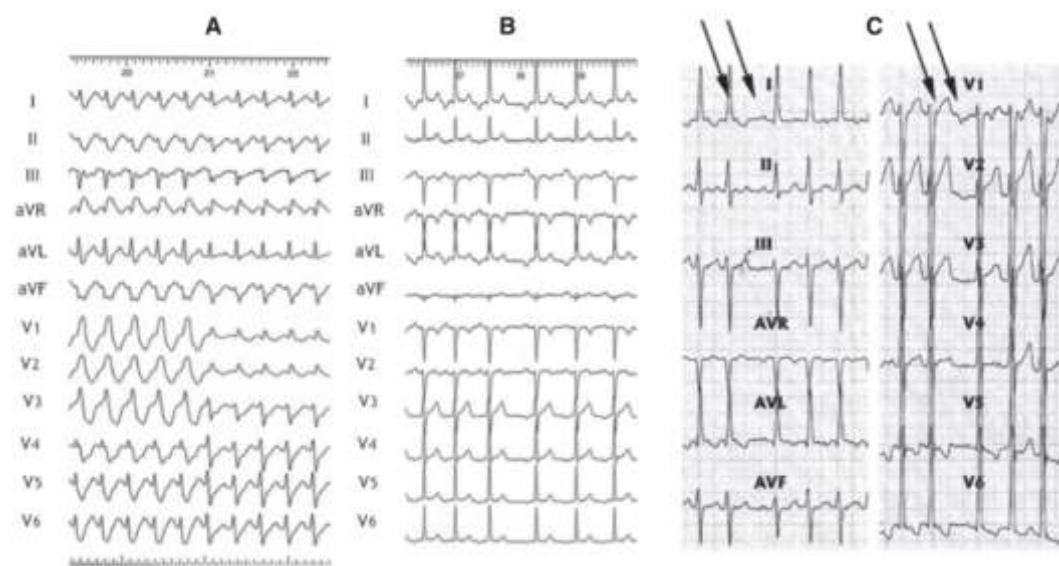


Figure 15-2: Focal atrial tachycardia. (A) Focal atrial tachycardia originating at the lateral right atrium conducted initially with full and then incomplete right branch bundle block aberration. (B) Focal atrial tachycardia originating at the left atrium (left superior pulmonary vein). (C) Focal atrial tachycardia from the right atrial appendage. Atrioventricular dissociation during carotid sinus massage (P waves indicated by arrows). **Source:** 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

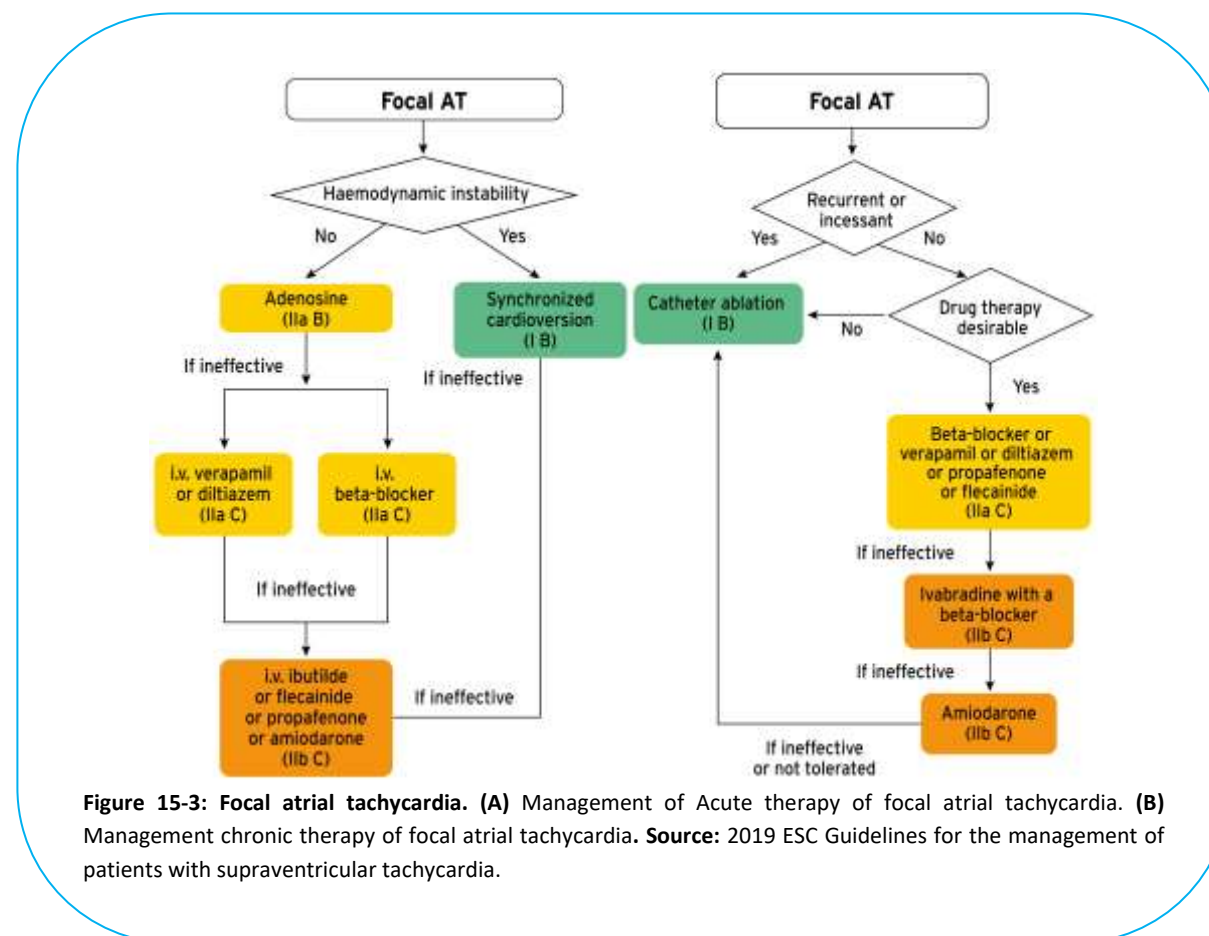
Table 15-5: ESC Recommendations for the therapy of focal atrial tachycardia:

| <i>Recommendation</i> | <i>Class Level</i> |
|---|--------------------|
| Acute therapy: | |
| <ul style="list-style-type: none"> ○ AT, particularly automatic AT, may be secondary to an acute illness that needs to be appropriately treated. ○ Drug therapy: <ul style="list-style-type: none"> - Adenosine, CCBs or β-blockers are mainly effective in triggered activity. - Adenosine and CCBs may suppress reentrant AT. | |

| | | |
|---|------------|----------|
| <ul style="list-style-type: none"> - β-blockers may suppress automatic AT (in up to 50% of cases). - Digoxin is better avoided, as it may initiate AT. ○ DC conversion is effective in reentrant and triggered-activity AT, but not in automatic AT. | | |
| Hemodynamically unstable patients: | | |
| <i>Synchronized DC cardioversion is recommended for hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients: | | |
| <i>Adenosine (6-18 mg i.v. bolus) should be considered ⁽¹⁾.</i> | IIa | B |
| <i>Beta-blockers (i.v. esmolol or metoprolol) should be considered in the absence of decompensated HF, if adenosine fails.</i> | IIa | C |
| <i>Verapamil or diltiazem (i.v.) should be considered for hemodynamically stable patients in the absence of hypotension or HFrEF, if adenosine fails.</i> | IIa | C |
| <i>If the above measures fail, the following may be used:</i> <ul style="list-style-type: none"> - i.v. ibutilide or - i.v. flecainide or propafenone or - i.v. amiodarone. | IIb | C |
| <i>Synchronized DC cardioversion is recommended when drug therapy fails to convert or control the tachycardia.</i> | I | B |
| Chronic therapy: | | |
| <i>Catheter ablation is recommended for recurrent focal AT, especially if incessant or causing TCM.</i> | I | B |

(1) Through its inhibition of cAMP generation, adenosine terminates atrial tachycardia secondary to triggered activity, and may transiently suppress atrial tachycardia secondary to automaticity by hyperpolarizing the myocardium. Its overall efficacy in the termination of AT varies between 10% and 80%.

| | | |
|---|------------|----------|
| <i>Beta-blockers or non-dihydropyridine CCBs (verapamil or diltiazem in the absence of HFrEF), or propafenone or flecainide (in the absence of structural or ischaemic heart disease), should be considered if ablation is not desirable or feasible.</i> | IIa | C |
| <i>Ivabradine with a beta-blocker may be considered if the above measures fail.</i> | IIb | C |
| <i>Amiodarone may be considered if the above measures fail.</i> | IIb | C |



Multifocal atrial tachycardia:

Multifocal AT is defined as a rapid, irregular rhythm with at least 3 distinct morphologies of P waves on the surface ECG ⁽¹⁾. Multifocal AT is commonly associated with underlying conditions, including pulmonary disease, pulmonary hypertension, coronary disease, and valvular heart disease, as well as hypomagnesaemia and theophylline therapy. It may also be seen in healthy infants under 1 year of age, and carries a good prognosis in the absence of underlying cardiac disease. MAT is frequently preceded or followed by AF or Aflutter.

| Table 15-6: ESC Recommendations for the therapy of multifocal atrial tachycardia | | |
|--|-------|-------|
| Recommendation | Class | Level |
| Acute therapy: | | |
| <i>Treatment of an underlying condition is recommended as a first step, if feasible.</i> | I | C |
| <i>I.V. beta-blockers, or i.v. non-dihydropyridine calcium channel blockers (verapamil or diltiazem) should be considered.</i> | IIa | B |
| Chronic therapy: | | |
| <i>Oral verapamil or diltiazem or selective beta-blocker should be considered for patients with recurrent symptomatic multifocal AT in the absence of HFrEF.</i> | IIa | B |
| <i>AV nodal ablation followed by pacing (preferable biventricular or His-bundle pacing) should be considered for patients with LV dysfunction due to recurrent multifocal AT refractory to drug therapy.</i> | IIa | C |

(1) If the atrial rate is < 100 bpm, the rhythm is called wandering atrial pacemaker **or** multifocal atrial rhythm.

Macro-re-entrant atrial tachycardias (MRAT):

Atrial flutter may be:

A. Cavotricuspid isthmus (CTI)-dependent flutter: a macro-reentry circuit around the tricuspid annulus using the CTI (narrow isthmus bordered by the IVC and crista terminalis posteriorly and the tricuspid annulus anteriorly) as a critical passage at the inferior boundary:

- **Typical flutter:** is the most frequent. This activation is also known as *counter-clockwise* when seen from the apex.
- **Reverse typical flutter:** When the circuit is activated in the opposite direction, i.e. clockwise, it results in a different ECG pattern.

B. Non-CTI dependant MRAT (Atypical flutter) may occur either in the right atrium usually after surgery for congenital heart defects or in the left atrium usually after ablation procedures. Progressive atrial degeneration or fibrosis may also be a cause. The circuit is smaller than the isthmus-dependent flutter, which means the reentrant loop is crossed more quickly, leading to a faster rate and smaller flutter waves on the ECG.

▪ **Electrophysiological features:**

In order to be sustained, the Aflutter must travel slowly across the CTI, such that the initially excited area recovers its excitability by the time it is reached again, and gets reactivated. This large area of excitability is called the excitable gap. This excitable gap allows a premature stimulus or atrial pacing to initiate Aflutter, but also to terminate it. That is how overdrive atrial pacing can penetrate the Aflutter circuit and break it.

▪ **Underlying pathology:**

A large proportion of Aflutter episodes (up to 60%) are triggered by an acute, possibly reversible predisposing event, such as surgery (especially cardiac or thoracic surgery) or acute medical or pulmonary illness (e.g., pneumonia, PE, COPD exacerbation). The remaining patients have underlying cardiac or pulmonary disease (HF is most common, COPD is second most common). Lone Aflutter (i.e., Aflutter without any comorbidity) is less common than lone AF.

- **ECG:**

The ECG is characterized by regular sawtooth atrial waves ⁽¹⁾. Flutter waves are negative in leads II, III, and aVF (due to the retrograde activation of the left atrium) and are positive in lead V1. In clockwise Aflutter, flutter waves are negative in V1 and positive in the inferior leads.

The typical Aflutter rate is 240–350 per minute. A rate as low as 200 may be consistent with a slow Aflutter and is seen in the case of RA enlargement (wherein the Aflutter circuit is longer) **or** if drug therapy with class I antiarrhythmic agents is used (slows the conduction across the loop).

Aflutter is usually conducted in a 2:1 fashion (two flutter waves for one QRS: ventricular rate ~150 bpm). Conduction may be 4:1 in case of AV nodal disease or rate-slowing drug therapy. 1:1 AV conduction may be seen in patients with accessory pathways or in patients with a slow flutter rate, particularly patients receiving class I antiarrhythmic drugs.

- **Association between Aflutter and AF:**

Aflutter is seen in 25-35% of AF patients.

In some cases, Aflutter waves abut remodeled LA areas with dispersed repolarization, degenerating into multiple small reentries and wavelets (= AF).

Occasionally, AF may organize along the CTI into Aflutter when treated with class Ic drugs or with amiodarone. In this subgroup, CTI ablation with continuation of the Ic drug often results in control of both AF and Aflutter.

In patients whose predominant rhythm is Aflutter, i.e., Aflutter episodes are more often documented on ECGs and Holter monitoring than AF, Aflutter ablation may prevent AF (occurrence of AF after CTI ablation is only 8% at 20 ± 14 months). Conversely, for those with a predominant Aflutter but a history of AF, the recurrence rate of AF is 38%, whereas for those with a predominant AF, the recurrence rate of AF is 86%.

- **Difference between Aflutter and AT:**

Aflutter is due to macroreentry. Conversely, AT is due to microreentry or other mechanisms.

(1) In leads II, III, and aVF, the flutter waves do not return to an isoelectric baseline between the deflections, which gives the sawtooth morphology. In V1, the positive waves may return to the isoelectric baseline (since lead V1 overlies the RA, it mainly “sees” the local RA activity).

For practical purposes, AT is distinguished from Aflutter by the following: **(1)** An atrial rate < 200 per minute is AT, whereas an atrial rate > 200-240 per minute is Aflutter; **(2)** AT is a focal rhythm, and thus, an isoelectric line is seen between P waves; Aflutter is a macroreentry with constant atrial activity and no isoelectric line.

It is important to differentiate AT from a slow Aflutter, for the following two reasons:

- The mechanism is different. Aflutter implies macroreentry and is often isthmus-dependent and easily cured with ablation. AT is less easily mapped and ablated, but may be broken by class I antiarrhythmics, β -blockers and CCBs.
- Aflutter is associated with a thromboembolic risk and requires anticoagulation, whereas AT, by itself, may not mandate anticoagulation. However, in older patients, AT is frequently associated with AF/Aflutter.

▪ **Management:**

| Table 15-7: ESC Recommendations for the therapy of macro-re-entrant atrial arrhythmias: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Anticoagulation, as in AF, is recommended for patients with atrial flutter and concomitant AF.</i> | I | B |
| <i>Patients with atrial flutter without AF should be considered for anticoagulation, but the threshold for initiation has not been established.</i> | IIa | C |
| Acute therapy: | | |
| <i>Acutely, Aflutter is managed like AF (rate control, anticoagulation). Approximately 55% of Aflutter episodes convert spontaneously, especially in the first 24–48 hours. If not: Perform TEE to rule out LA thrombus then cardiovert.</i> | | |
| Haemodynamically unstable patients: | | |
| <i>Synchronized DC cardioversion is recommended for hemodynamically unstable patients.</i> | I | B |
| Haemodynamically stable patients: | | |
| <i>i.v. ibutilide or i.v. or oral (in-hospital) dofetilide are recommended for conversion to sinus rhythm.</i> | I | B |

| | | |
|--|------------|----------|
| <i>Low-energy (≤ 100 J biphasic) electrical cardioversion is recommended for conversion to sinus rhythm.</i> | I | B |
| <i>High-rate atrial pacing ⁽¹⁾ is recommended for termination of atrial flutter in the presence of an implanted pacemaker or defibrillator.</i> | I | B |
| <i>i.v. beta-blockers or non-dihydropyridine CCBs (verapamil or diltiazem), should be considered for control of rapid ventricular rate.</i> | IIa | B |
| <i>Invasive and non-invasive high-rate atrial pacing may be considered for termination of atrial flutter.</i> | IIb | B |
| <i>i.v. amiodarone may be tried if the above are not available or desirable.</i> | IIb | C |
| <i>Propafenone and flecainide are not recommended for conversion to sinus rhythm ⁽²⁾.</i> | III | B |
| Chronic therapy: | | |
| <i>Catheter ablation is recommended for:</i> <ul style="list-style-type: none"> - Symptomatic, recurrent episodes of atrial flutter or - Persistent atrial flutter or - in the presence of depressed LV systolic function due to TCM. | I | B |
| <i>Catheter ablation should be considered after the first episode of symptomatic typical atrial flutter.</i> | IIa | B |
| <i>Beta-blockers or non-dihydropyridine calcium channel blockers (verapamil or diltiazem, in the absence HFrEF) should be considered if ablation is not desirable or feasible.</i> | IIa | C |

(1) Perform overdrive atrial pacing at a rate 60-100 bpm higher than the flutter rate, i.e., an atrial rate of ~400. This is done in the setting of dual-chamber PM, or in the post-cardiac-surgery setting when temporary atrial pacing wires are in place.

(2) Class I drugs (especially Ic) are not helpful for Aflutter therapy. Drugs that slow the conduction across the CTI increase the excitable gap and allow Aflutter to perpetuate rather than terminate. Even worse, by slowing the reentrant circuit, they slow the atrial rate, which allows more atrial impulses to be conducted through the AV node. They convert 2:1 Aflutter into 1:1 Aflutter.

| | | |
|--|------------|----------|
| <i>Amiodarone may be considered to maintain sinus rhythm if the above measures fail.</i> | IIb | C |
| <i>AV nodal ablation with subsequent pacing ('ablate and pace'), either biventricular or His bundle pacing, should be considered if all the above fail and the patient has symptomatic persistent macro-re-entrant atrial arrhythmias with fast ventricular rates.</i> | IIa | C |

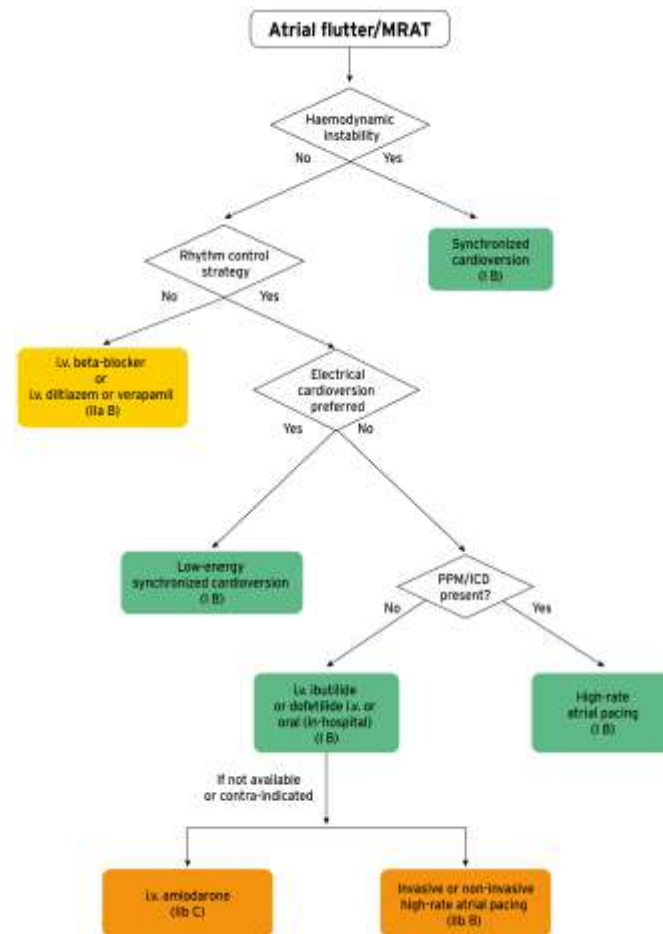


Figure 15-4: Acute therapy of stable atrial flutter or macro-re-entrant atrial tachycardia. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

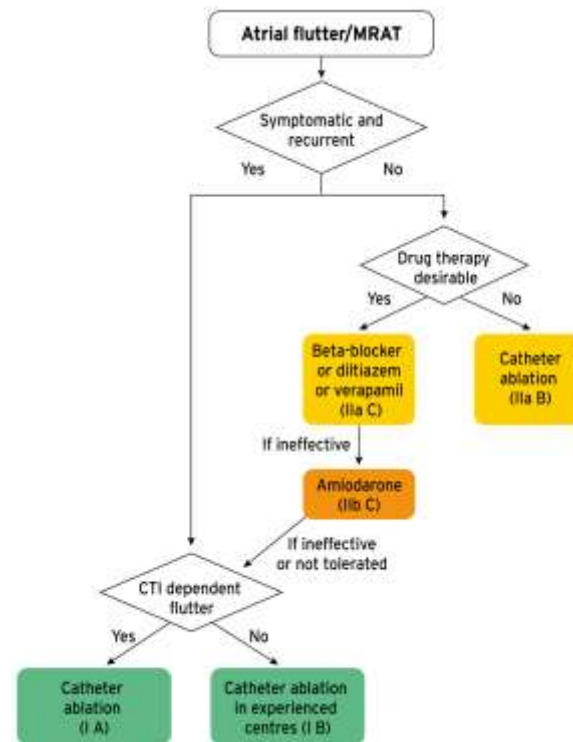


Figure 15-5: Chronic therapy of stable atrial flutter or macro-re-entrant atrial tachycardia. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

Atrioventricular junctional arrhythmias:

The most common form of AV junctional arrhythmias is atrioventricular nodal re-entrant tachycardia (AVNRT). AVNRT usually occurs in patients without underlying heart disease.

Non-re-entrant junctional tachycardias are relatively rare, the most common being junctional ectopic tachycardia, usually seen as a congenital arrhythmia or, more often, early after infant open heart surgery.

▪ **Mechanism:**

- Approximately 20% of normal individuals have dual AV node pathways: fast pathway and slow pathway, but most of them do not manifest AVNRT.

Normally, the AV node conducts impulses through the fast pathway. *The fast pathway conducts faster but has a longer refractory period than the slow pathway.*

- After a PAC, the fast pathway may still be in its refractory period, whereas the slow pathway, having the short refractory period, has already recovered and conducts forward. The impulse then conducts retrogradely through the fast pathway if it has recovered; this leads to a **typical "slow-then-fast" ("SF")** AVNRT "Over 95% of all cases". If the fast pathway has not recovered its refractory period, the impulse will lead to one QRS having a longer PR interval; arrhythmia is not initiated.

- Other, less common forms of AVNRT are the **atypical "fast-then-slow", and "slow-then-slow"** AVNRT. In the fast-then-slow AVNRT, the slow pathway has a longer refractory period than the fast pathway.

In atypical AVNRT, the distinction between "fast-slow" and "slow-slow" forms is of no practical significance and certain cases of atypical AVNRT cannot be classified according to described criteria.

Table 15-8: Classification of AVNRT types:

| | HA | VA ⁽¹⁾ (His) | AH/HA interval |
|-----------------------|---------|-------------------------|----------------|
| Typical AVNRT | ≤ 70 ms | ≤ 60 ms | > 1 |
| Atypical AVNRT | > 70 ms | > 60 ms | Variable |

▪ **ECG:**

- AVNRT typically manifests as a regular, narrow QRS complex tachycardia, with a ventricular rate of ~150-250 bpm (most often ~180 bpm).

(1) Ventriculoatrial interval measured from the onset of ventricular activation on surface ECG to the earliest deflection of the atrial activation on the His bundle electrogram.

P waves are retrograde and are usually hidden inside the QRS **or** at the terminal portion of the QRS. P waves are often simultaneous to the QRS and therefore are clearly visible in only ~1/2 of the cases. These P waves manifest as terminal r' in V1 and pseudo-S in the inferior leads, with short RP (often < 90 ms).

Rarely, P waves may precede QRS, with a short PR interval < 110 ms.

If P waves cannot be identified in patients presenting with a regular narrow complex tachycardia, AVNRT is the most likely diagnosis.

- The tachycardia being initiated by an ectopic atrial beat that goes down the slow pathway, the PR interval of this initial beat is longer than the sinus PR interval.

As opposed to automatic atrial tachycardia, this initial ectopic P wave usually differs from the subsequent (retrograde) P waves and does not march out with them.

- The atypical forms of AVNRT (fast-slow **or** slow-slow AVNRT) have a long RP interval, longer than 1/2 RR interval, and may thus simulate atrial tachycardia. The loop is overall slower than in typical AVNRT; thus, the atypical forms tend to be incessant tachycardias. Occasionally, dual AV nodal pathways manifest on the baseline sinus rhythm. In this case, two different PR intervals are seen in sinus rhythm.

| Table 15-9: ESC Recommendations for the management of AVNRT: | | |
|---|-------|-------|
| Recommendation | Class | Level |
| Acute therapy: | | |
| Hemodynamically unstable patients: | | |
| Synchronized DC cardioversion is recommended for hemodynamically unstable patients. | I | B |
| Hemodynamically stable patients: | | |
| Vagal maneuvers, preferably in the supine position with leg elevation, are recommended. | I | B |
| Adenosine (6-18 mg i.v. bolus) is recommended if vagal maneuvers fail ⁽¹⁾ . | I | B |

(1) Adenosine breaks AVNRT and AVRT by blocking the AV node. AVNRT and AVRT are the main arrhythmias that break rather than simply slow down with adenosine

| | | |
|---|------------|----------|
| <i>Verapamil or diltiazem i.v. should be considered if vagal maneuvers and adenosine fail.</i> | Ila | B |
| <i>Beta-blockers (i.v. esmolol or metoprolol) should be considered if vagal maneuvers and adenosine fail.</i> | Ila | C |
| <i>Synchronized DC cardioversion is recommended when drug therapy fails to convert or control the tachycardia.</i> | I | B |
| Chronic therapy: | | |
| <i>Catheter ablation (of the slow pathway) is recommended for symptomatic, recurrent AVNRT ⁽¹⁾.</i> | I | B |
| <i>Diltiazem or verapamil, in patients without HFrEF, or beta-blockers should be considered if ablation is not desirable or feasible.</i> | Ila | B |
| <i>Abstinence from therapy should be considered for minimally symptomatic patients with very infrequent, short-lived episodes of tachycardia.</i> | Ila | C |

N.B:

In AVNRT, the atria and ventricles are not required for AV nodal reentry. Thus, if a PAC, a PVC, or atrial or ventricular pacing does not penetrate the AV nodal reentry, AVNRT will not be disrupted.

(1) Anatomically, the slow pathway is located inferiorly, along the tricuspid annulus in front of the coronary sinus os, whereas the fast pathway is located superior to the coronary sinus os. They both coalesce more distally to form the compact AV node then His, which is located anteriorly. So Catheter ablation can now be accomplished in both typical and atypical AVNRT with almost no risk of AV block by targeting the inferior nodal extension, and avoiding the mid-septum and the roof of the coronary sinus.

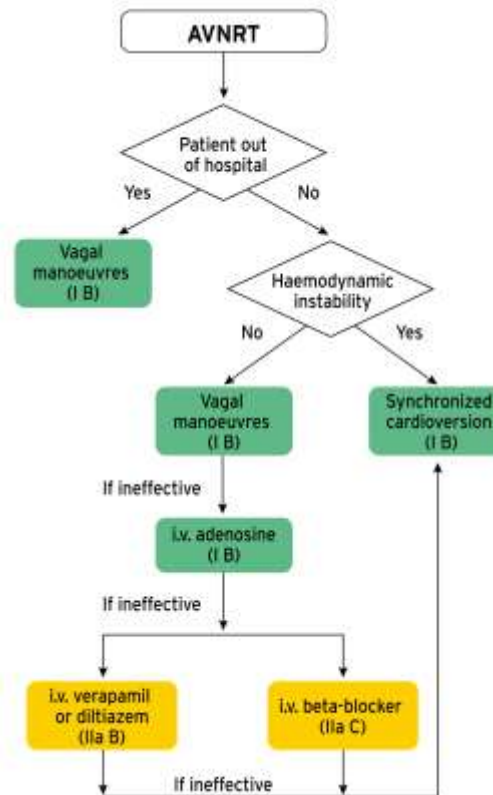


Figure 15-6: Acute therapy of atrioventricular nodal re-entrant tachycardia. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

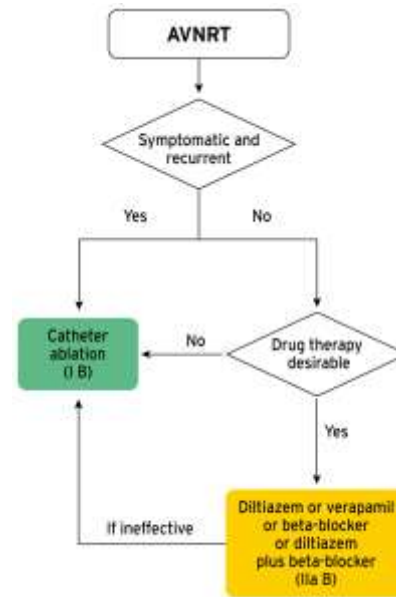


Figure 15-7: Chronic therapy of AVNRT. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

Atrioventricular arrhythmias:

▪ Pathophysiology:

Atrioventricular tachycardia (AVRT) uses an anatomically defined re-entrant circuit that consists of two limbs: **first**, the atrioventricular node and His-purkinje system (AVN-HPS), and **second**, an accessory pathway (AP). The two limbs are characterized by differences in refractoriness and conduction times, with critically timed premature atrial or ventricular beats initiating re-entrant tachycardia. On rare occasions, the circuit consists of two APs.

- Accessory pathways (APs) are single or multiple strands of myocardial cells that bypass the physiological conduction system, and directly connect atrial and ventricular myocardium.

- APs may be:
 - **Manifest/overt pathways** (Most diagnosed APs): Those APs can conduct both antegradely (i.e from the atrium to the ventricle) and retrogradely (i.e from the ventricle to the atrium). The manifest AP conducts faster than the AV node. Antegradely conducted PAC down the AP bypassing the slower AV nodal conduction results in (**Antidromic AVRT**). Retrogradely conducted PVC or very early PAC through the AP results in (**orthodromic AVRT**). Of tachycardias occurring with a manifest pathway, 75% are orthodromic AVRTs, 5% are antidromic AVRTs, and ~20% are pre-excited AF or atrial flutter.
 - **Concealed pathways** (30% of diagnosed APs): Those APs can only conduct retrogradely from the ventricle to the atrium. A concealed AP is silent when the patient is in sinus rhythm and only manifests itself during a tachycardia that involves its retrograde conduction (**orthodromic AVRT**) ⁽¹⁾.
- This AP “pre-excites” the ventricles and the phenomenon is called pre-excitation. **WPW pattern** is used to describe the baseline pre-excitation, while **WPW syndrome** is used when arrhythmias occur as a result of the manifest AP. WPW pattern is seen in ~0.2% of the population. It has a higher prevalence in Ebstein’s anomaly and HOCM.
- **ECG:**
 - Baseline ECG is affected by a manifest accessory pathway (pre-excitation or WPW pattern). The baseline resting ECG is characterized by:
 - Short PR interval (≤ 120 ms). The pre-excited PR is shorter than the AV nodal conduction but may not be short in the absolute sense.
 - Slurred upstroke (or downstroke) of the QRS complex (‘delta wave’) ⁽²⁾, which corresponds to the early onset of ventricular activation through the AP; and

(1) As opposed to AVNRT, in orthodromic AVRT the atria and the ventricles are depolarized sequentially rather than simultaneously and distinct P waves are almost always seen, with a short RP interval $< 1/2$ RR, but not too short (> 90 ms).

(2) As opposed to RBBB and LBBB, QRS is slurred and delayed in its initial rather than terminal portion.

- Wide QRS complex (> 120 ms) with secondary ST-T abnormalities (directed opposite to QRS) ⁽¹⁾.
- Baseline ECG is not affected by a concealed accessory pathway, as the pathway cannot conduct antegradely, and therefore it does not conduct during sinus rhythm; no delta wave is seen.

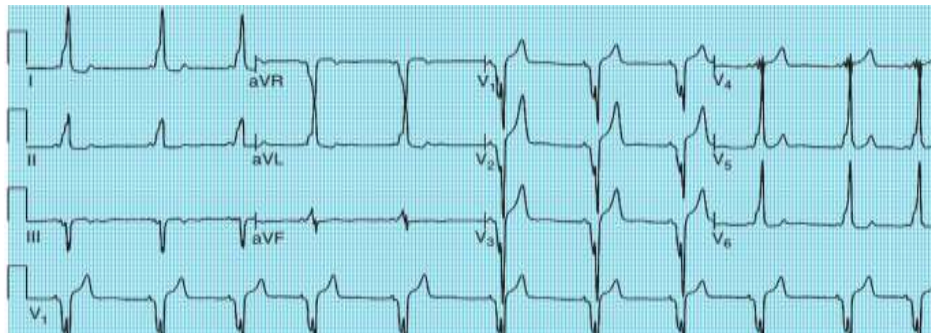


Figure 15-8: Wolff-Parkinson-White pattern. This 12-lead ECG shows preexcitation with right-sided accessory pathway connecting the RA to the RV. It shows the typical characteristics of WPW pattern, including a short PR interval, wide QRS complex, and a delta wave. **Source:** Olshansky, Brian, et al. Arrhythmia Essentials. Elsevier, 2017.

- **The degree of pre-excitation** depends on the relative amount of ventricular tissue stimulated through the AP versus the AV node, which depends on:
 - *The relative conduction speed through the AP versus the AV node.* PR may be normal and delta wave may be absent in patients who have a fast AV nodal conduction and a left lateral AP ⁽²⁾.

-
- (1)** QRS may be narrower than 120 ms in up to 50% of pre-excitation cases, whenever the ventricular excitation spreading down the AP does not occur long enough before the excitation spreading down the AV node.
 - (2)** In left lateral AP, it takes a long time for the atrial impulse to reach the atrial insertion of the AP, by which time a slick AV node would have stimulated most of the myocardium: an increasing amount of ventricular muscle is excited through the normal AV pathway and a decreasing amount is excited through the anomalous pathway, which results in a less pre-excited QRS complex.

- *The refractory period of the AP*, which is longer than the refractory period of the AV node. An AP with a long refractory period is more likely to block at a relatively slow heart rate (e.g., 100 bpm) ⁽¹⁾.
- When antegrade AP conduction and delta wave only manifest intermittently, or when the ECG criteria of pre-excitation are not completely fulfilled, pre-excitation and delta wave may be unveiled by:
 - *Slowing the conduction over the AV node* (e.g. adenosine, carotid sinus massage), which leads to proportionately larger amount of myocardium stimulated through the AP. This leads to a shorter PR interval and a wider delta wave.
 - *PAC*: Delta wave is typically wider during a PAC. PAC results in prolongation of the conduction time through the AV node, whereas the AP keeps a constant conduction time; thus, relatively more ventricular muscle gets excited through the AP.
 - *Rapid atrial pacing*: A similar phenomenon may be seen with progressively faster atrial pacing, wherein AV nodal conduction slows down allowing delta wave to become more prominent, until the AP refractory period is reached.

If, despite those maneuvers, the only abnormality seen on the ECG is a short PR interval, the patient simply has accelerated AV nodal conduction rather than pre-excitation. It was suggested previously that this may be due to an atriofascicular bypass tract, especially if the patient develops SVT (Long–Ganong–Levine syndrome). However, this is very rarely the case.

N.B:

- AVRT is the most common tachycardia associated with WPW syndrome. Patients with WPW are also prone to develop AF, possibly because of reentry around the atrial insertion of the AP (prevalence of AF in young patients with WPW ~15–30%). Also, any AVRT can trigger AF and become poorly tolerated. AF with fast ventricular response over an overt AP with a short anterograde refractory period is a potentially life-threatening arrhythmia in patients with WPW syndrome, due to potential degeneration into VF.

(1) *Always distinguish refractory period from conduction speed. AP can conduct very fast and lead to a very wide delta wave, yet have a long refractory period and thus block at a relatively slow heart rate. In this case, AP conducts the atrial waves fast, but cannot conduct too many atrial waves back-to-back. The A-to-V interval is short, but the V-to-V interval is not.*

➤ Permanent junctional reciprocating tachycardia is a rare form of AV reciprocating tachycardia using a concealed AP. Usually these APs, originally described by Coumel, are located in the posteroseptal region and are associated with retrograde decremental conduction properties.

▪ **Localization of the accessory pathway according to the baseline ECG:**

○ **There are four possible AP locations: (1)** Left lateral, free wall (the most common, ~50% of APs); **(2)** Right free wall (10–20%); **(3)** Posteroseptal (near the coronary sinus, 20-30%); **(4)** Anteroseptal (least common, ~5%). Approximately 5–10% of patients have multiple APs.

○ **How to localize AP?**

In order to localize the AP, it is key to **identify the leads with negative delta waves**. Delta is negative in the leads surrounding the origin of the AP, as AP will be pointing away from those leads. Analyze the right-sided lead V1, the inferior leads, and the left lateral leads I and aVL:

- **Lead V1** provides an assessment of right vs. left pathway. A negative delta in lead V1 (QS pattern) implies that AP is right-sided. A positive delta wave in lead V1 (R, RS, or RSr' pattern) implies a left-sided pathway.
- **The inferior leads** provide an assessment of anterior vs. inferior pathway. A negative delta in the inferior leads implies an AP is often a posteroseptal pathway.
- **The lateral leads (I, aVL)** provide an assessment of left lateral vs. septal or RV pathway. A negative delta wave in the left lateral leads often implies a left lateral pathway.

N.B: The same rules apply to localizing the origin of VT. The orientation of QRS is analyzed in those same leads. There is one additional rule in VT: negative QRS concordance in all precordial leads V1–V6 implies an apical origin, a pattern not seen with delta wave or pre-excited SVT.

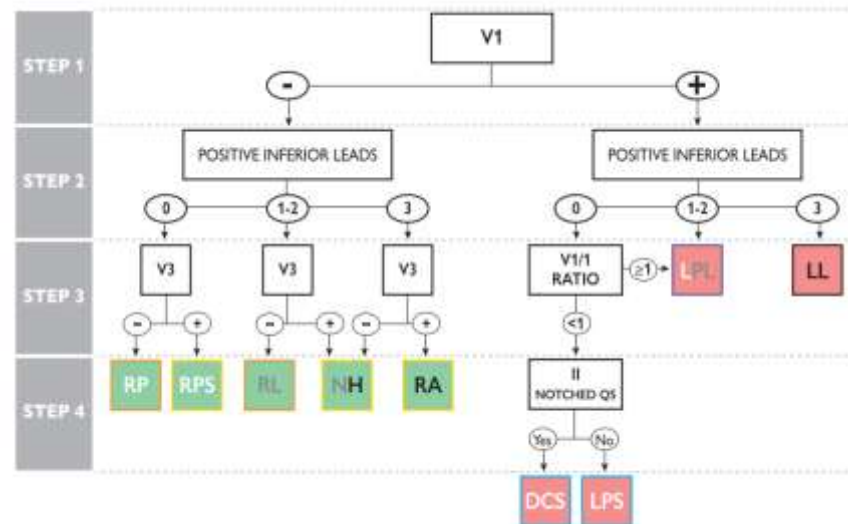


Figure 15-9: Localization of accessory pathways in the presence of maximum (spontaneous or evoked) pre-excitation. Accessory pathway locations are green when right-sided and red when left-sided. Left posterolateral accessory pathways can have 0, 1, or 2 inferior leads with positive polarity, whereas nodo-Hisian accessory pathways can have 1, 2, or 3 inferior leads with positive polarity. Right-sided accessory pathways are framed orange or yellow when the V3 lead is negative or positive, respectively. Left posterior accessory pathways are framed blue when the V1/I ratio is < 1 or purple when V1/I ratio is ≥ 1 . AP = accessory pathway; DCS = deep coronary sinus; LL = left lateral; LPL = left posterolateral; LPS = left paraseptal; NH = nodo-Hisian; RA = right anterior; RL = right lateral; RP = right posterior; RPS = right paraseptal. **Source:** 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

Management:

Table 15-10: ESC Recommendations for the therapy of atrioventricular re-entrant tachycardia due to manifest or concealed accessory pathways:

| Recommendation | Class | Level |
|----------------|-------|-------|
|----------------|-------|-------|

| | | |
|---|------------|----------|
| Acute therapy: | | |
| Hemodynamically unstable patients: | | |
| <i>Synchronized DC cardioversion is recommended for hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients: | | |
| <i>Vagal maneuvers, preferably in the supine position with leg elevation, are recommended.</i> | I | B |
| <i>In orthodromic AVRT,</i> | | |
| - Adenosine (6-18 mg i.v. bolus) is recommended if vagal maneuvers fail. | I | B |
| - I.V. verapamil or diltiazem should be considered if vagal maneuvers and adenosine fail. | IIa | B |
| - I.V. beta-blockers (esmolol or metoprolol) should be considered in the absence of decompensated HF, if vagal maneuvers and adenosine fail. | IIa | C |
| <i>In antidromic AVRT,</i> | | |
| - I.V. ibutilide or procainamide or i.v. flecainide or profenone ⁽¹⁾ or synchronized DC cardioversion should be considered if vagal manoeuvres and adenosine fail. | IIa | B |
| - I.V. amiodarone may be considered in refractory cases ⁽²⁾ . | IIb | B |
| <i>Synchronized DC cardioversion is recommended when drug therapy fails to convert or control the tachycardia.</i> | I | B |
| Chronic therapy: | | |
| <i>Catheter ablation of AP(s) is recommended in patients with symptomatic, recurrent AVRT.</i> | I | B |

(1) Intravenous class I or class III drugs (procainamide or ibutilide) may be used as they increase the AP's antegrade refractory period.

(2) In contrast to ESC guidelines, i.v amiodarone is contraindicated in the ACC guidelines, as acute amiodarone has a β -blocker effect and may block the AV node more than the AP (conversely, chronic amiodarone may be used, as it increases the AP's refractory period).

| | | |
|--|------------|----------|
| <i>Beta-blockers or non-dihydropyridine CCBs (verapamil or diltiazem in the absence of HFrEF) should be considered if no signs of pre-excitation are present on resting ECG, if ablation is not desirable or feasible.</i> | IIa | B |
| <i>Propafenone or flecainide may be considered in patients with AVRT and without ischemic or structural heart disease, if ablation is not desirable or feasible ⁽¹⁾.</i> | IIb | B |
| <i>Digoxin, beta-blockers, diltiazem, verapamil, and amiodarone are not recommended and are potentially harmful in patients with pre-excited AF.</i> | III | B |

(1) Antiarrhythmic drugs class I (flecainide or propafenone), amiodarone, and sotalol increase the antegrade and retrograde refractory periods across the accessory pathway. However, by increasing the antegrade refractory period, they increase the difference in refractory period between the AV node and AP, making it easier for a PAC to initiate orthodromic AVRT. Combining a β -blocker with the antiarrhythmic drug may circumvent this phenomenon. This is also less likely to occur with antiarrhythmic agents that have an AV nodal blocking effect (amiodarone or sotalol).

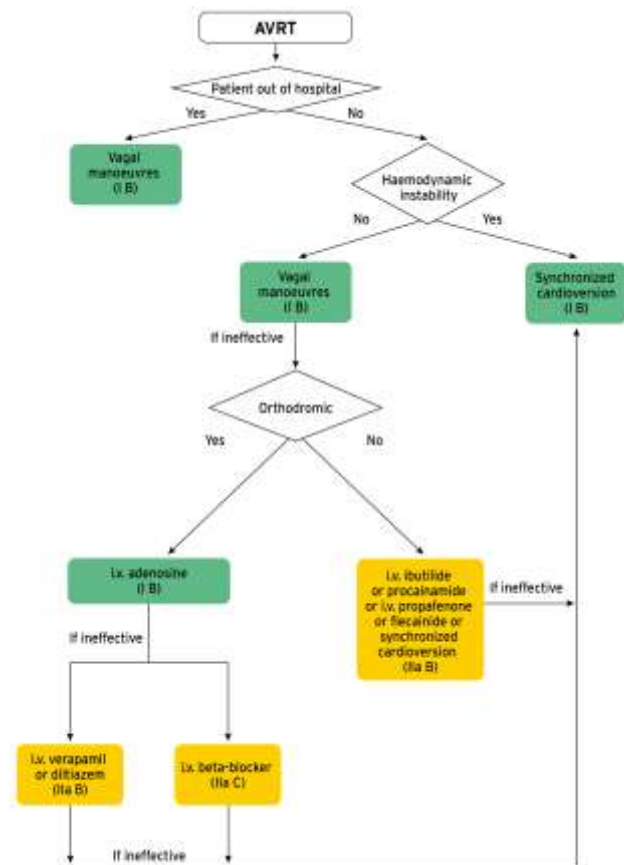


Figure 15-10: Acute therapy of atrioventricular re-entrant tachycardia. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

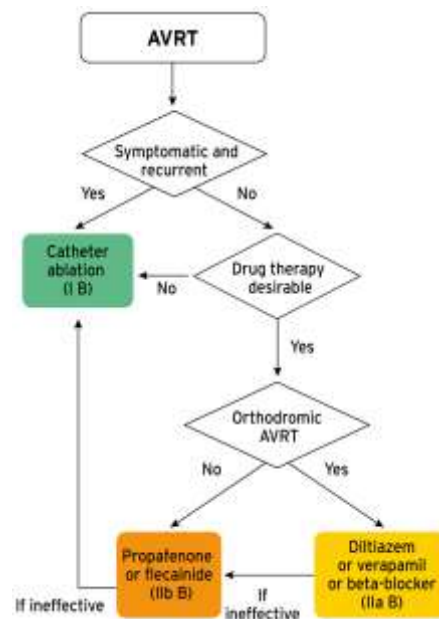


Figure 15-11: Chronic therapy of atrioventricular re-entrant tachycardia. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

- Acute therapy of pre-excited AF:

Table 15-11: ESC Recommendation for Acute therapy of pre-excited AF:

| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| Hemodynamically unstable patients: | | |
| <i>Synchronized DC cardioversion is recommended in hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients: | | |
| <i>Ibutilide or procainamide (i.v.) should be considered.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>Flecainide or propafenone (i.v.) may be considered.</i> | IIb | B |
| <i>Synchronized DC cardioversion is recommended if drug therapy fails to convert or control the tachycardia.</i> | I | B |
| <i>Amiodarone (i.v.) is not recommended.</i> | III | B |

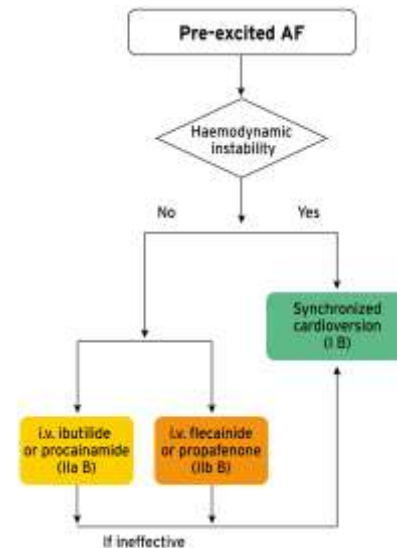


Figure 15-12: Acute therapy of pre-excited AF. Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

- **Management of asymptomatic pre-excitation:**

- Patients with asymptomatic pre-excitation may be at a potential risk of sudden cardiac death, and should be subjected to a risk stratification process. The risk of sudden death is low (< 1% per 10 years), but may be higher, up to 0.5% per year in some subgroups.

- The risk of sudden death does not depend on how fast the AP conducts the atrial waves, as by definition the AP has a fast conduction; what is more important is how many back-to-back atrial waves the AP can conduct, which depends on the AP refractory period.
- Every asymptomatic patient should undergo either an invasive (EP testing) or a non-invasive assessment (exercise testing) of the refractory period of the AP:
 - **During exercise testing**, an accessory pathway with a long refractory period will not be able to antegradely conduct. Thus, complete and abrupt loss of pre-excitation during exercise testing confirms a long AP refractory period. (delta wave may be lost because of increased AV nodal conduction during exercise rather than a block in the AP).
 - **EP testing with the use of isoprenaline** consists of inducing AF or using rapid atrial pacing to measure the shortest pre-excited R–R interval (SPERRI). The best predictor of sudden death is the assessment of the SPERRI during AF \leq 250 ms.

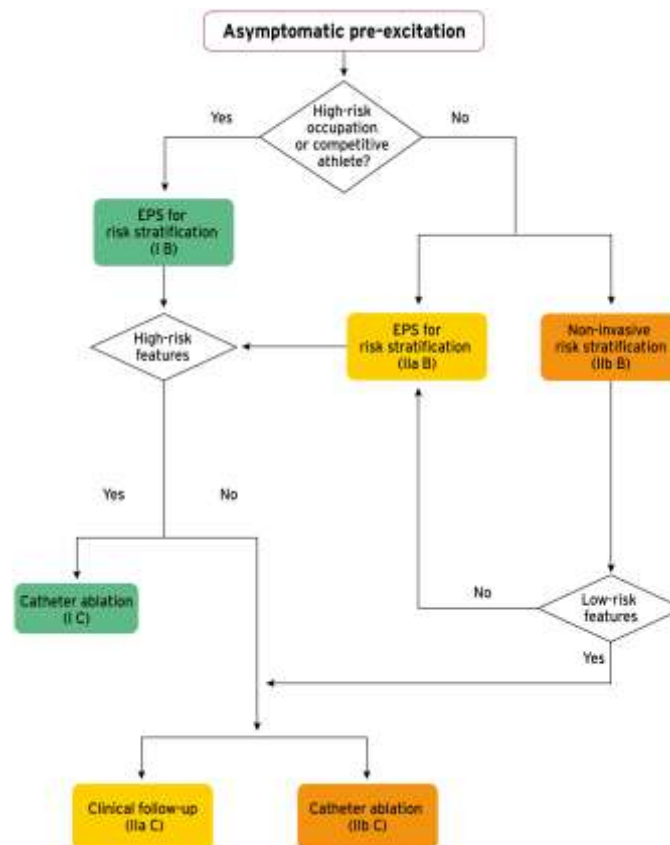


Figure 15-13: Risk stratification and therapy of patients with asymptomatic pre-excitation.

High-risk features at EP study are: shortest preexcited RR interval during AF ≤ 250 ms, accessory pathway effective refractory period ≤ 250 ms, multiple accessory pathways, and inducible AVRT.

Low-risk features at non-invasive risk stratification are: induced or intermittent loss of pre-excitation on exercise or drug testing, resting ECG, and ambulatory ECG monitoring.

Source: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.

Table 15-12: ESC Recommendations for the Management of patients with asymptomatic pre-excitation:

| Recommendation | Class | Level |
|--|--------------|--------------|
| <i>Performance of an EPS, with the use of isoprenaline, is recommended to risk stratify individuals with asymptomatic pre-excitation who have high-risk occupations/hobbies ⁽¹⁾, and those who participate in competitive athletics.</i> | I | B |
| <i>Performance of an EPS to risk stratify individuals with asymptomatic pre-excitation should be considered.</i> | IIa | B |
| <i>Catheter ablation is recommended in asymptomatic patients in whom electrophysiology testing with the use of isoprenaline identifies high-risk properties, such as (1) shortest pre-excited R-R interval (SPERRI) ≤ 250 ms, (2) AP effective refractory period (ERP) ≤ 250 ms, (3) multiple APs, and (4) an inducible AP-mediated tachycardia.</i> | I | B |
| <i>Catheter ablation is recommended in high-risk patients with asymptomatic pre-excitation after discussing the risks, especially of heart block associated with ablation of anteroseptal or mid-septal APs, and benefits of the procedure.</i> | I | C |
| <i>Non-invasive evaluation of the conducting properties of the AP in individuals with asymptomatic pre-excitation may be considered.</i> | IIb | B |
| <i>Invasive risk stratification with an EPS is recommended in patients without 'low-risk' characteristics at non-invasive risk stratification.</i> | I | C |
| <i>Clinical follow-up should be considered in a patient with asymptomatic pre-excitation and a low-risk AP at invasive risk stratification.</i> | IIa | C |
| <i>Catheter ablation should be considered in patients with asymptomatic pre-excitation and LV dysfunction due to electrical dyssynchrony.</i> | IIa | C |

(1) Such as pilots and professional drivers.

| | | |
|---|------------|----------|
| <i>Catheter ablation may be considered in a patient with asymptomatic pre-excitation, and a low-risk AP at invasive or non-invasive risk stratification ⁽¹⁾.</i> | IIb | C |
| <i>Catheter ablation may be considered in patients with low-risk asymptomatic pre-excitation in appropriately experienced centres according to patient preferences.</i> | IIb | C |

SVT in specific circumstances:

▪ **SVT in adults with congenital heart disease:**

Alongside HF, cardiac arrhythmias are a common late complication in adults with congenital heart defects. This is due to the underlying cardiac defect, previous or persisting hemodynamic issues, and previous surgical interventions resulting in myocardial damage and scarring. Diagnosis and treatment of arrhythmias in ACHD patients is complicated by the unusual nature of tachycardia, complex intracardiac anatomy, and especially by difficulties in accessing the heart, for example due to abnormal venous anatomy (e.g. azygos continuity or previous Fontan operation). As a consequence, specific expertise in patients with ACHD and access to adequate electrophysiological tools are required when performing catheter ablation procedures in these patients.

| Table 15-13: ESC Recommendations for the therapy of supraventricular tachycardia in congenital heart disease in adults: | | |
|--|--------------|--------------|
| Recommendation | Class | Level |
| <i>Anticoagulation for focal AT or atrial flutter should be similar to that for patients with AF.</i> | I | C |
| Acute therapy: | | |
| Hemodynamically unstable patients: | | |

(1) The mortality risk associated with ablation is low (< 0.05%) and lower than the yearly risk of sudden cardiac death, which may justify AP ablation in these asymptomatic patients.

| | | |
|--|------------|----------|
| <i>Synchronized DC cardioversion is recommended for hemodynamically unstable patients.</i> | I | B |
| Hemodynamically stable patients: | | |
| <i>Vagal maneuvers, preferably in the supine position with leg elevation, are recommended.</i> | I | B |
| <i>Adenosine (6-18 mg i.v. bolus) is recommended if vagal maneuvers fail.</i> | I | B |
| <i>i.v. verapamil or diltiazem should be considered, if vagal maneuvers and adenosine fail.</i> | IIa | B |
| <i>i.v. beta-blockers (esmolol or metoprolol) should be considered if vagal maneuvers and adenosine fail.</i> | IIa | C |
| <i>Synchronized DC cardioversion is recommended when drug therapy fails to convert or control the tachycardia.</i> | I | B |
| Chronic therapy: | | |
| <i>Catheter ablation in experienced centres should be considered.</i> | IIa | C |
| <i>Beta-blockers should be considered for recurrent focal AT or atrial flutter, if ablation is not possible or successful.</i> | IIa | C |
| <i>In patients with SVT planned for surgical repair of a congenital heart disease anomaly, pre-operative catheter ablation or intraoperative surgical ablation should be considered.</i> | IIa | C |
| <i>Amiodarone may be considered for prevention if ablation is not possible or successful.</i> | IIb | C |
| <i>Sotalol is not recommended as a first-line antiarrhythmic drug as it is related to an increased risk of pro-arrhythmias and mortality.</i> | III | C |
| <i>Flecainide and propafenone are not recommended as first-line antiarrhythmic drugs in patients with ventricular dysfunction and severe fibrosis.</i> | III | C |

▪ **SVT in pregnancy:**

SVT is associated with an increased risk of death during pregnancy. Although most of the exacerbations of SVT during pregnancy are benign and can be treated effectively with standard medical therapy, the circumstances that should be considered include the well-being of the foetus and the effects on labour, delivery, and lactation.

Catheter ablation should be postponed to the second trimester, if possible, but may be necessary in the case of drug-refractory and poorly tolerated tachycardia. It should then be performed at an experienced centre using non-fluoroscopic electroanatomical mapping and catheter navigation systems.

Ideally, Catheter ablation should therefore be considered before pregnancy when possible in patients with a known history of symptomatic tachyarrhythmia.

Electrical cardioversion should be the first choice when arrhythmias are hemodynamically unstable.

| Table 15-14: ESC Recommendations for the therapy of supraventricular tachycardia in pregnancy: | | |
|---|--------------|--------------|
| Recommendation | Class | Level |
| <i>Catheter ablation is recommended in symptomatic women with recurrent SVT who plan to become pregnant.</i> | I | C |
| Acute therapy: | | |
| <i>Immediate electrical cardioversion is recommended for any tachycardia with hemodynamic instability.</i> | I | C |
| <i>Vagal manoeuvres and, if these fail, adenosine are recommended for acute conversion of SVT.</i> | I | C |
| <i>An i.v. beta-1 selective blocker (except atenolol) should be considered for acute conversion or rate control of SVT.</i> | IIa | C |
| <i>i.v. digoxin should be considered for rate control of AT if beta-blockers fail.</i> | IIa | C |
| <i>i.v. ibutilide may be considered for termination of atrial flutter.</i> | IIb | C |
| Chronic therapy: | | |

| | | |
|--|------------|----------|
| <i>During the first trimester of pregnancy, it is recommended that all antiarrhythmic drugs should be avoided, if possible.</i> | I | C |
| <i>Beta-1 selective (except atenolol) beta-blockers or verapamil, in order of preference, should be considered for prevention of SVT in patients without WPW syndrome.</i> | IIa | C |
| <i>Flecainide or propafenone should be considered for prevention of SVT in patients with WPW syndrome, and without ischaemic or structural heart disease.</i> | IIa | C |
| <i>Flecainide or propafenone in patients without structural heart disease should be considered if AV nodal blocking agents fail to prevent SVT.</i> | IIa | C |
| <i>Digoxin or verapamil should be considered for rate control of AT if beta-blockers fail in patients without WPW syndrome.</i> | IIa | C |
| <i>Amiodarone is not recommended in pregnant women.</i> | III | C |
| <i>Fluoroleless catheter ablation should be considered in cases of drug-refractory or poorly tolerated SVT, in experienced centres.</i> | IIa | C |

▪ **SVT in sports:**

Athletes with frequent supraventricular arrhythmias should be assessed to exclude the presence of an underlying cardiac disease, electrolyte imbalance, thyroid dysfunction, and the use of stimulants or performance-enhancing drugs.

Table 15-15: ESC Recommendations for sports participation in athletes with ventricular pre-excitation and supraventricular arrhythmias:

| Criteria for eligibility | | Eligibility |
|-------------------------------|--|-------------------|
| Premature atrial beats | <i>No symptoms, no cardiac disease</i> | <i>All sports</i> |

| | | |
|---|---|---|
| AVRT or AF in the context of WPW syndrome | <i>Ablation is mandatory. Sports are allowed 1 month after ablation if there are no recurrences</i> | <i>All sports</i> |
| Asymptomatic ventricular pre excitation | <i>Ablation is mandatory in patients at high risk. Sports are allowed 1 month after ablation if there are no recurrences</i> | <i>All sports</i> |
| Paroxysmal SVT (AVNRT, AVRT over a concealed AP, and AT) | <i>Ablation is recommended. Sports are allowed 1 month after ablation if there are no recurrences. Ablation undesirable or not feasible</i> | <i>All sports All sports, except those with high intrinsic risk of loss of consciousness</i> |

▪ **SVT and driving restrictions:**

Table 15-16: European Working Group 2013 report on driving and cardiovascular disease: driving in arrhythmias and conduction disorders: SVT

| | Group 1 | Group 2 |
|-----------------------------------|---|---|
| Arrhythmia | drivers of motorcycles, cars, and other small vehicles with and without a trailer | drivers of vehicles > 3500 kg or passenger carrying vehicles exceeding eight seats excluding the driver |
| AF/atrial flutter/focal AT | <i>Driving may continue provided no history of syncope. If history of syncope, driving must cease until the condition has been satisfactorily controlled/treated.</i> | <i>Driving may continue provided no history of syncope and anticoagulation guidelines are adhered to. If history of syncope, driving must cease unless the underlying cause is treated and the risk of recurrence is low.</i> |

| | | |
|-----------------------------|--|---|
| | | <i>Rate control during tachycardia should be adequate. Driving can only be resumed after medical assessment.</i> |
| AVNRT, AVRT, and WPW | <i>If history of syncope, driving must cease until the condition has been satisfactorily controlled/treated.</i> | <i>Driving may continue provided no history of syncope or other significant symptoms (e.g. palpitations with dizziness).</i> <i>If so, driving must cease until the underlying cause is treated so that the risk of recurrence is low.</i> <i>In case of pre-excitation, driving may only be allowed after specialist assessment.</i> |

References and suggested readings:

- Josep Brugada, Demosthenes G Katritsis, Elena Arbelo, et al., ESC Scientific Document Group, 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC): Developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC), *European Heart Journal*, Volume 41, Issue 5, 1 February 2020, Pages 655–720
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- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier.
- Olshansky, Brian, et al. Arrhythmia Essentials. Elsevier, 2017.
- <https://litfl.com/ecg-library>

Chapter 16:

Atrial Fibrillation

Definition and Diagnosis:

Clinical AF: Symptomatic or asymptomatic AF that is documented by surface ECG (Lasting For at least 30 sec, or entire 12-lead ECG).

| Table 16-1: ESC Recommendations for diagnosis of AF: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>ECG documentation is required to establish the diagnosis of AF.</i> | I | B |
| <i>A standard 12-lead ECG recording or a single-lead ECG tracing of ≥ 30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.</i> | | |

Mechanism of AF initiation:

AF requires a trigger that initiates the arrhythmia and a substrate that sustains it. The most common triggers are premature atrial beats originating from the pulmonary veins. Atrial stretch and atrial fibrosis shorten the atrial effective refractory period and disrupt the electrical interconnections between the muscle bundles, causing local conduction heterogeneity. This allows ectopic activity originating from the pulmonary veins or elsewhere to get conducted and initiate multiple microreentry cycles (atrial wavelets). The autonomic system may contribute to the initiation of AF, i.e., an increase in the sympathetic or parasympathetic drive may trigger ectopy in the pulmonary veins and AF.

The most frequent histopathological feature of AF is atrial fibrosis, which may precede the onset of AF. Atrial dilatation is present in over 50% of patients with AF and may be not only a cause but also a consequence of AF. Atrial electrical remodeling, i.e., progressive shortening of the effective refractory period, further explains how prolonged AF makes restoring and maintaining sinus rhythm less likely (“AF begets AF”).

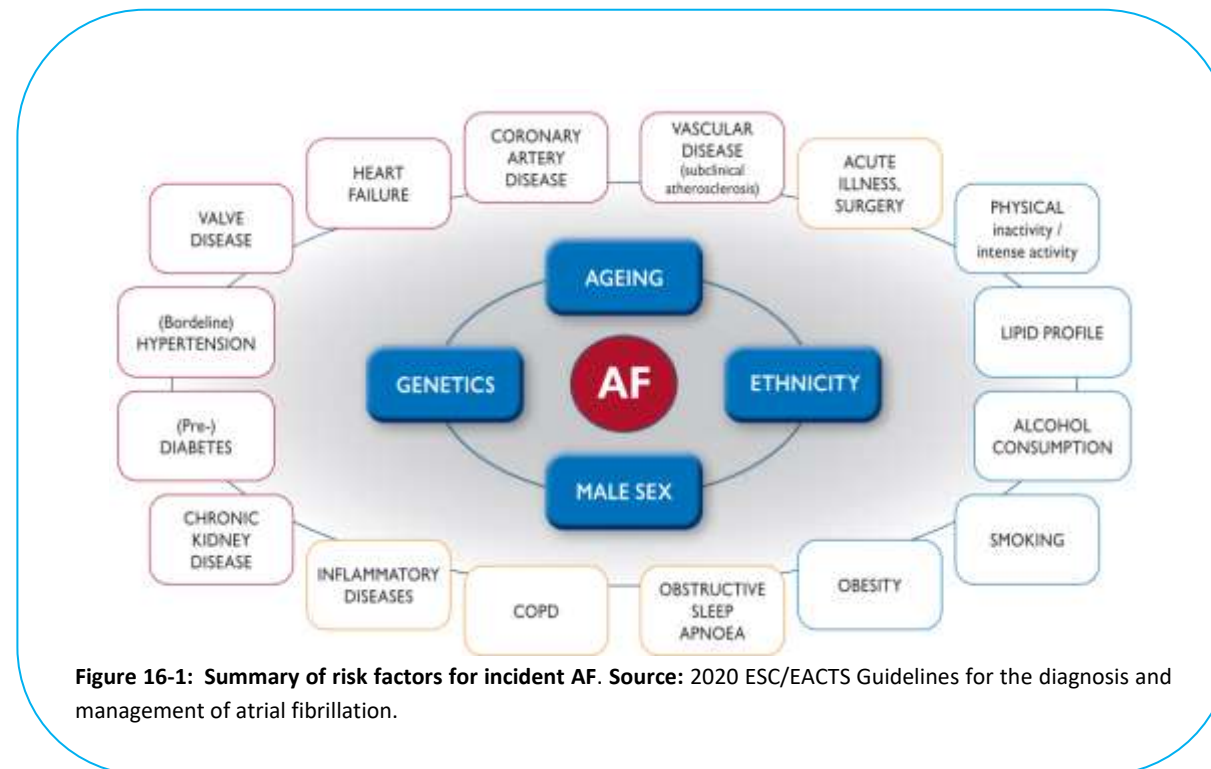
Screening for AF:

Table 16-2: ESC Recommendations for screening to detect AF:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Opportunistic screening for AF (by pulse taking or ECG rhythm strip): | | |
| - is recommended in patients ≥ 65 years of age. | I | B |
| - is recommended in hypertensive patients. | I | B |
| - should be considered in patients with OSA. | IIa | C |
| Systematic ECG screening should be considered to detect AF in individuals aged ≥ 75 years, or those at high risk of stroke. | IIa | B |
| <i>It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.</i> | I | B |
| <i>When screening for AF it is recommended that:</i> | I | B |
| - The individuals undergoing screening are informed about the significance and treatment implications of detecting AF. | | |
| - A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF. | | |
| - Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of ≥ 30 s or 12-lead ECG and confirms that it shows AF. | | |

Epidemiology:

Worldwide, AF is the most common sustained cardiac arrhythmia in adults. The currently estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF. Its prevalence increases with age: 3-4% of patients aged 65-75 have AF and 10% of patients aged 80 years or older have AF.



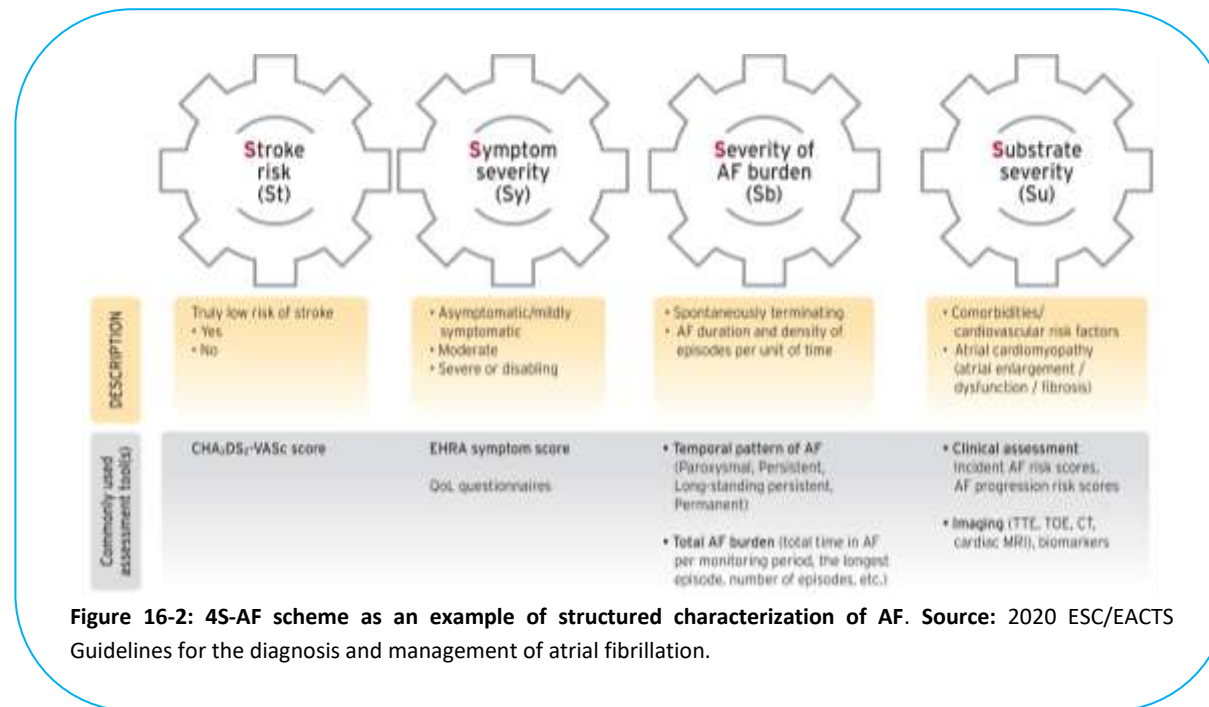
AF subtypes, burden, and progression:

Traditionally, five patterns of AF are distinguished, based on presentation, duration and spontaneous termination of AF episodes. Despite practicality, this classification has significant limitations, and the recommendations for AF management are not based solely on the temporal AF patterns.

| Table 16-3: Classification of AF: | |
|---------------------------------------|--|
| AF pattern | Definition |
| First diagnosed | <i>AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.</i> |
| Paroxysmal | <i>AF that terminates spontaneously or with intervention within 7 days of onset.</i> |
| Persistent | <i>AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥ 7 days</i> |
| Long-standing persistent | <i>Continuous AF of > 12 months' duration when decided to adopt a rhythm control strategy.</i> |
| Permanent | <i>AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken.</i> <i>Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be reclassified as 'long-standing persistent AF'.</i> |
| Terminology that should be abandoned: | |

| | |
|---------------------------------|---|
| Lone AF | <i>A historical descriptor. Increasing knowledge about the pathophysiology of AF shows that in every patient a cause is present. Hence, this term is potentially confusing and should be abandoned.</i> |
| Valvular/non valvular AF | <i>Differentiates patients with moderate/severe mitral stenosis and those with mechanical prosthetic heart valve(s) from other patients with AF, but may be confusing and should not be used.</i> |
| Chronic AF | <i>Has variable definitions and should not be used to describe populations of AF patients.</i> |

As a tool to streamline the assessment of AF patients at different healthcare levels, inform treatment decision-making and facilitate optimal management of AF patients, the 2020 ESC AF guidelines introduce the 4S-AF scheme for characterization of AF that considers stroke risk, severity of symptoms, severity of AF burden and severity of substrate.



Clinical features:

- **Clinical presentation:** Patients with AF may have various symptoms but 50-87% are initially asymptomatic.

| Table 16-4: ESC Recommendations for diagnostic evaluation of patients with AF: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <p><i>In patients with AF, it is recommended to:</i></p> <ul style="list-style-type: none"> - Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment. | I | C |

- Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.

Table 16-5: EHRA symptom scale:

| Score | Symptoms | Description |
|-----------|-----------|--|
| 1 | None | <i>AF does not cause any symptoms.</i> |
| 2a | Mild | <i>Normal daily activity not affected by symptoms related to AF.</i> |
| 2b | Moderate | <i>Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms.</i> |
| 3 | Severe | <i>Normal daily activity affected by symptoms related to AF.</i> |
| 4 | Disabling | <i>Normal daily activity discontinued.</i> |

• **AF-related outcomes:**

There are four main consequences of AF: **(i)** thrombus formation in the left atrial appendage followed by thrombus embolization, **(ii)** fast heart rate which leads to compromised ventricular filling, **(iii)** loss of the atrial kick that contributes to up to 40% of the cardiac output in stable HF patients, **(iv)** rhythm irregularity, per se, reduces cardiac output compared to a similar rate that is regular.

AF is related to the following outcomes:

Table 16-6: AF-related outcomes:

| Outcome | Incidence in AF | Mechanism |
|---------------|--|--|
| Death | two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men, with an overall 3.5-fold mortality risk increase | HF (14.5%), malignancy (23.1%), and infection/sepsis (17.3%), whereas stroke-related mortality was only 6.5% |
| Stroke | - 20-30% of ischemic strokes | - Cardioembolic |

| | | |
|---------------------------------|--|--|
| | - 10% of cryptogenic strokes | - Related to comorbid vascular atheroma. |
| LV dysfunction | - HF is present in 34% of AF patients. - AF is present in 4% of patients with HF NYHA I and 50% of patients with NYHA IV have AF. | - AF-related atrial myopathy <u>or</u> - by tachycardic heart rates <u>or</u> - by AF-related impaired systolic Ca^{2+} handling in LV cardiomyocytes. |
| Dementia | HR 1.4-1.6 (irrespective of stroke history) | - Brain white matter lesions, inflammation - Hypoperfusion, Microembolism |
| Depression | Depression in 16-20% of AF patients (Even suicidal ideation) | - Severe symptoms and decrease QoL - Drug side effects |
| Impaired Quality of life | - > 60% of patients have impaired QoL - 17% have disabling symptoms. | - Related to AF burden, comorbidities, psychological functioning and medication. - Distressed personality type (Type D) |
| Hospitalization | 10-40% annual hospitalization rate | - AF management, related to HF, MI or AF related symptoms. - Treatment associated complications |

Management (ABC pathway):

The simple Atrial fibrillation Better Care (ABC) holistic pathway ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimization) streamlines integrated care of AF patients. Compared with usual care, implementation of the ABC pathway has been significantly associated with lower risk of all cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization, lower rates of cardiovascular events, and lower health-related costs.

▪ **'A' = Anticoagulation/Avoid stroke:**

The annual risk of stroke in patients with AF not receiving any antithrombotic therapy ranges from 1% to 18%, and averages ~5% per year. Therefore, OAC is a main pillar in the management of AF patients.

For assessment of stroke risk, a risk factor-based approach is recommended, using the CHA₂DS₂-VASc clinical stroke risk score to initially identify “low stroke risk” patients who should not be offered antithrombotic therapy. In most populations (excluding patients with mechanical heart valves or moderate to severe mitral stenosis) that are eligible for OAC, NOACs are preferred to vitamin K antagonists.

| Table 16-7: CHA ₂ DS ₂ -VASc score: | | | |
|---|---|----------|--|
| Risk factors | | Points | Comment |
| C | Congestive heart failure <ul style="list-style-type: none"> - Clinical HF, or - Objective evidence of moderate to severe LV dysfunction, or - HCM | 1 | <i>Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), <u>or</u> the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging; HCM confers a high stroke risk and OAC is beneficial.</i> |
| H | Hypertension <i>or on antihypertensive therapy</i> | 1 | <i>History of hypertension may result in vascular changes that predispose to stroke, and a well controlled BP today may not be well-controlled over time. The optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120-129/< 80 mmHg.</i> |
| A | Age ≥ 75 years | 2 | <i>Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards. Age related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥75 years.</i> |

| | | | |
|-----------------------|---|----------|---|
| D | Diabetes mellitus - Treatment with oral hypoglycaemic drugs and/or insulin or - fasting blood glucose > 125 mg/dL (7 mmol/L) | 1 | <i>DM is a well-established risk factor for stroke, and more recently stroke risk has been related to: duration of DM and presence of diabetic target organ damage, e.g. retinopathy. Both type 1 and type 2 DM confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged < 65 years with type 2 DM compared to patients with type 1 DM.</i> |
| S | Stroke Previous stroke, TIA, or thromboembolism | 2 | <i>Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.</i> |
| V | Vascular disease - Angiographically significant CAD, - Previous MI, - PAD, or - Aortic plaque | 1 | <i>Vascular disease (PAD or MI) confers a 17 - 22% excess risk, particularly in Asian patients. Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients. Complex aortic plaque, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke.</i> |
| A | Age 65-74 years | 1 | <i>See above. Recent data from Asia suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA2DS2-VASc score may be used in Asian patients.</i> |
| S c | Sex category (female) | 1 | <i>A stroke risk modifier rather than a risk factor</i> |
| Maximum score: | | | 9 |

○ **Left atrial appendage closure:**

- Surgical closure of the left atrial appendage (ligation, stapling, or excision) may be considered in AF patients undergoing valvular surgery or CABG. Ligation or stapling of the appendage, or even excision, is incomplete in up to 60% of patients, leaving a residual stump or flow on TEE, hence the residual stroke risk (incomplete appendage ligation may increase clot formation).
- Another alternative to chronic anticoagulation is percutaneous closure of the LA appendage (e.g., Watchman device). Compared to warfarin, Watchman is associated with more embolic strokes and less hemorrhagic strokes, resulting in a similar all-cause stroke risk; and less major hemorrhage and CV mortality. Caveats: early procedural hazard (tamponade), short-term requirement for warfarin (6 weeks) + clopidogrel (6 months), and long-term requirement for aspirin. In light of the safety of NOACs, the role of Watchman device is limited (class IIb); it may be used in patients with increased long-term bleeding risk but not those with contraindication to anticoagulation, as antithrombotic regimen is required for 6 months after implantation.

| Table 16-8: Left atrial appendage occlusion and exclusion: | | | |
|---|--|--|--|
| | Watchman/low bleeding risk | Watchman/high bleeding risk | ACP/Amulet |
| Aspirin | 75 – 325 mg/day Indefinitely | | |
| OAC | <i>Start warfarin after procedure (target INR 2-3) until 45 days or continue until adequate LAA sealing is confirmed by TOE (< 5 mm leak). NOAC is possible alternative</i> | <i>None</i> | |
| Clopidogrel | <i>Start 75 mg/day when OAC stopped, continue until 6 months after the procedure</i> | <i>75 mg/day for 1 - 6 months while ensuring adequate LAA sealing</i> | |
| Comments | <i>Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)</i> | <i>Clopidogrel often given for shorter time in very high-risk situations</i> | <i>Clopidogrel may replace aspirin if better tolerated</i> |

Note: Load aspirin or clopidogrel before procedure if untreated.

Heparin with activated clotting time (ACT) > 250 seconds before or immediately after trans-septal punctures for all patients, followed by LMWH when warfarin needed.

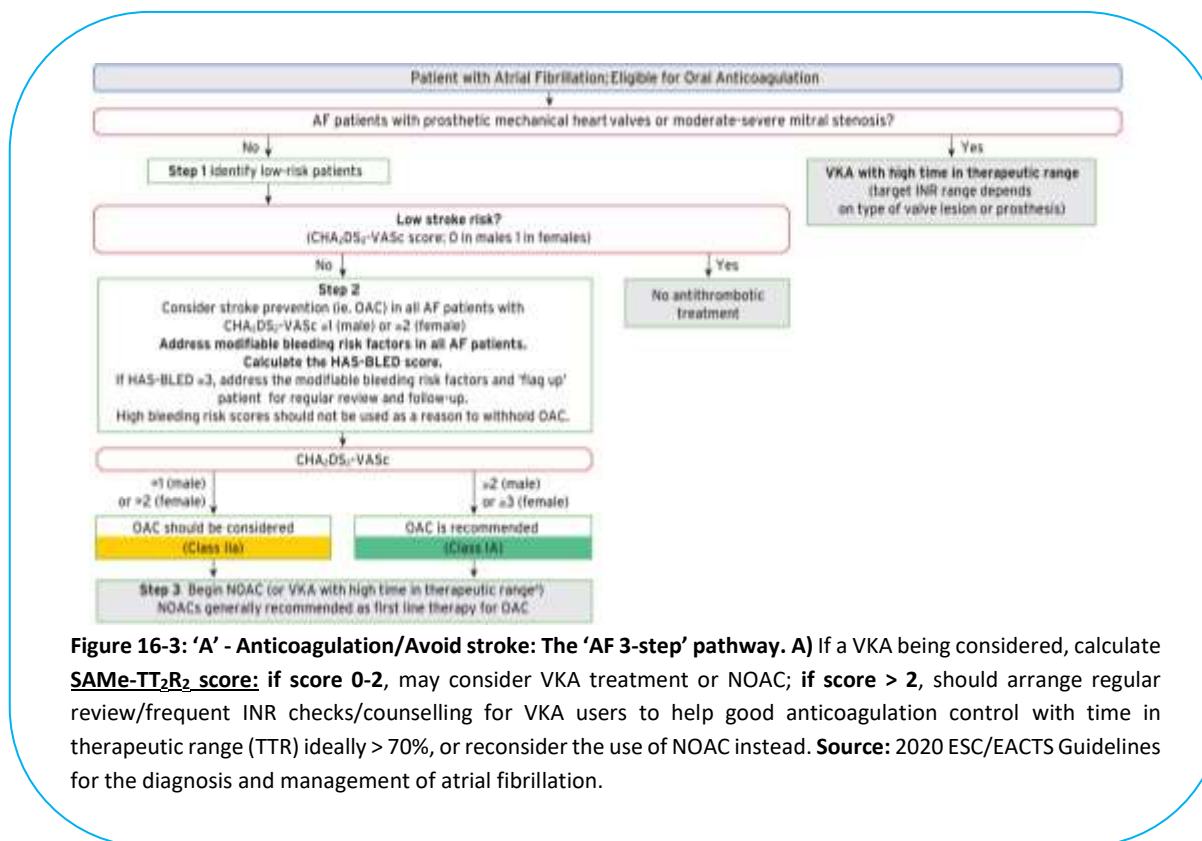


Table 16-9: ESC Recommendations for the prevention of thrombo-embolic events in AF:

| Recommendations | Class | Level |
|-----------------|-------|-------|
|-----------------|-------|-------|

| | | |
|--|------------|----------|
| <i>For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis)</i> | I | A |
| <i>For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA₂DS₂-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA₂DS₂-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy</i> | I | A |
| <i>OAC is recommended for stroke prevention in AF patients with CHA₂DS₂-VASc score ≥ 2 in men or ≥ 3 in women.</i> | I | A |
| <i>OAC should be considered for stroke prevention in AF patients with a CHA₂DS₂-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences.</i> | IIa | B |
| <i>For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify nonmodifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.</i> | I | B |
| <i>For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow-up.</i> | IIa | B |
| <i>Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.</i> | I | B |
| <i>In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation.</i> | IIa | B |
| <i>If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR $\geq 70\%$.</i> | I | B |

| | | |
|---|------------|----------|
| <i>In patients on VKAs with low time in INR therapeutic range (e.g., TTR < 70%), recommended options are:</i> | | |
| <i>- Switching to a NOAC but ensuring good adherence and persistence with therapy; or</i> | I | B |
| <i>- Efforts to improve TTR (e.g., education/counselling and more frequent INR checks)</i> | IIa | B |
| <i>Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.</i> | III | A |
| <i>Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention ⁽¹⁾</i> | III | A |
| <i>Clinical pattern of AF (i.e., first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.</i> | III | A |
| <i>NOACs are contraindicated in patients with a prosthetic mechanical valve ⁽²⁾.</i> | III | B |
| <i>Use of NOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis.</i> | III | C |
| Recommendations for occlusion or exclusion of the LAA: | | |

(1) Patients with a high HAS-BLED score usually have a high CHA₂DS₂-VASc score and a high stroke risk, the absolute stroke risk increasing more sharply than the bleeding risk. Thus, these patients derive an even greater net clinical benefit from anticoagulation than patients with a low HAS-BLED score and should generally receive anticoagulation.

(2) NOACs have not been studied in valvular AF (i.e., AF with mitral stenosis or valvular mechanical prosthesis). Dabigatran has been studied with mechanical prosthetic valves (RE-ALIGN study) and was associated with a drastic increase in thromboembolic events (5% at 3 months). In fact, an overwhelming activation of the factor VII pathway, after contact with tissue factor expressed at the site of tissue or endothelial injury, may generate more thrombin than dabigatran can inhibit; warfarin may be more effective, as it blocks factor VII activation, in addition to the intrinsic (factor IX) and common pathways (factor X and thrombin). On the other hand, NOACs may be used in moderate/severe valvular disease that is not MS as the landmark trials included moderate/severe MR, AI, AS, TR. Also, landmark trials of apixaban and edoxaban included patients with bioprosthetic valves and suggested their efficacy in this small subgroup. RIVER trial proved the efficacy of rivaroxaban in AF with mitral bioprosthesis.

| | | |
|---|------------|----------|
| <i>LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).</i> | IIb | B |
| <i>Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.</i> | IIb | C |

| Table 16-10: Clinical risk factors in the HAS-BLED score: | | |
|--|---|-------------------------|
| Risk factors and definitions | | Points awarded |
| H | Uncontrolled hypertension (SBP > 160 mmHg) | 1 |
| A | Abnormal renal and/or hepatic function (Dialysis, transplant, serum creatinine > 200 mmol/L, cirrhosis, bilirubin ≥ 2 ULN, AST/ALT/ALP > 3 x ULN) | 1 point for each |
| S | Stroke (Previous ischaemic or haemorrhagic stroke ⁽¹⁾) | 1 |
| B | Bleeding history or predisposition (Previous major haemorrhage or anaemia or severe thrombocytopenia) | 1 |
| L | Labile INR ⁽²⁾ (TTR < 60% in patient receiving VKA) | 1 |
| E | Elderly (Aged > 65 years or extreme frailty) | 1 |
| D | Drugs or excessive alcohol drinking (Concomitant use of antiplatelet or NSAID; and/or excessive ⁽³⁾ alcohol per week) | 1 point for each |

(1) Haemorrhagic stroke would also score 1 point under the 'B' criterion.

(2) Only relevant if patient receiving a VKA.

(3) Alcohol excess or abuse refers to a high intake (e.g. > 14 units/week), where the clinician assesses there would be an impact on health or bleeding risk.

Maximum Score**9****Score 0-1** = Low risk.**Score 2** = Intermediate risk**Score ≥ 3** = High risk A high HAS-BLED score ≥ 3 is indicative of the need for regular clinical review and follow up, but should not be used per se as a reason for stopping oral anticoagulation.**▪ 'B' Better symptom control:**

Control of symptoms is the second pillar of the ABC pathway and crucial for patients management. Symptoms control consists of both rate control and rhythm control.

• Rate control:

- The optimal target heart rate is still unclear. In symptomatic patients, the goal of therapy was to reduce heart rate to < 80 bpm at rest (AFFIRM and RACE trials). However, in the RACE II trial, this strict rate control (resting heart rate < 80) did not offer any benefit over a more lenient control (a resting heart rate < 110 bpm) in patients with permanent AF and mild or no AF-related symptoms. Although strict rate control improves outcomes in systolic HF with sinus rhythm, this is not the case in systolic HF with AF or in HFrEF. A higher rate is necessary to compensate for the loss of atrial contribution to stroke volume; also, nocturnal pauses that accompany tight rate control may be particularly harmful in HF (induce VT, low flow). For AF associated with HF, the target rate control remains < 100 bpm rather than < 80 bpm (based on RACE-II substudy, substudies of β -blockers in HF, and Swedish HF registry).
- Pharmacological rate control can be achieved with beta-blockers, digoxin, diltiazem, and verapamil, or combination therapy. The choice of rate control drugs in the individual patient is driven by the comorbidities.
- AV node ablation achieves effective rate control heart rate in patients that are unresponsive or intolerant to drug treatment.

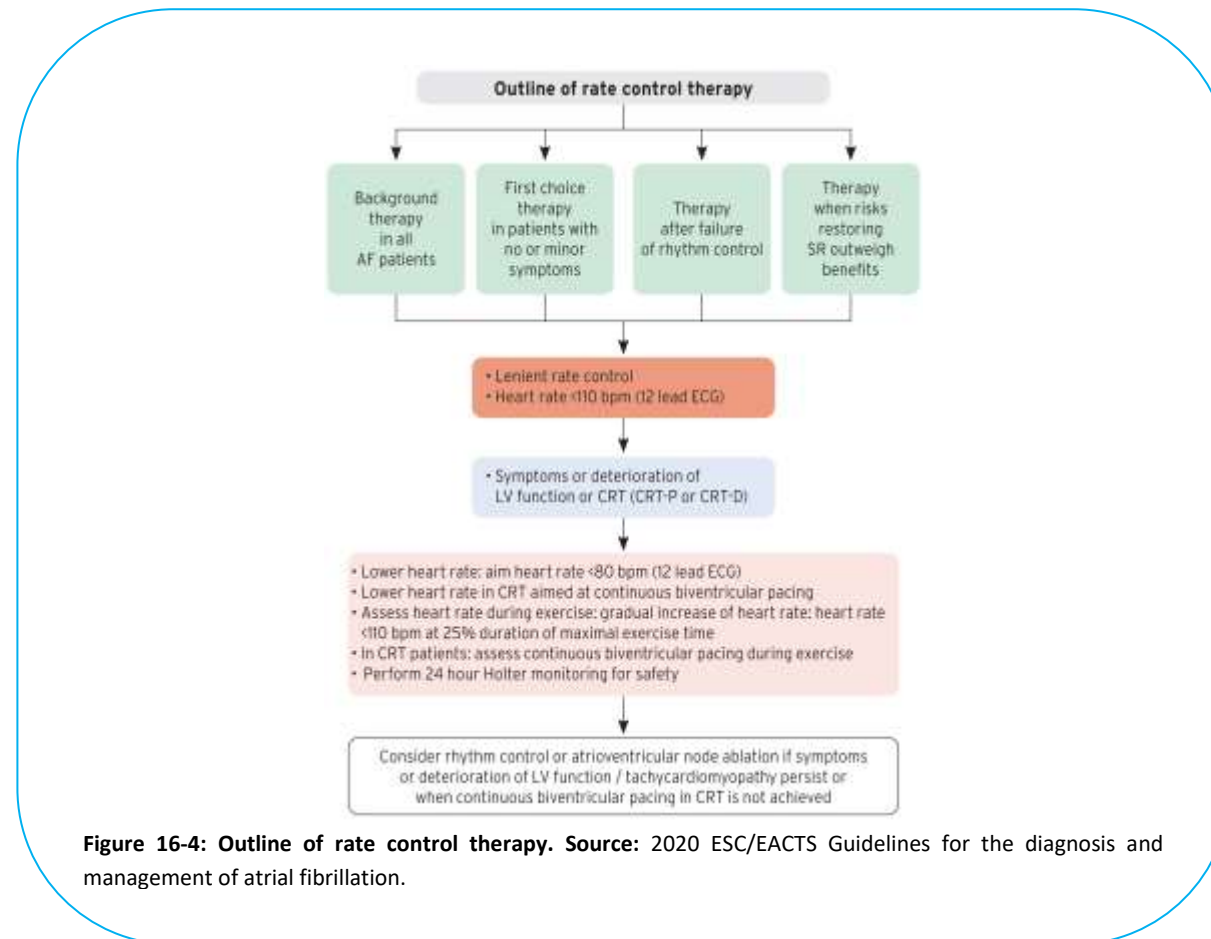


Figure 16-4: Outline of rate control therapy. Source: 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

○ Choice of rate control drugs:

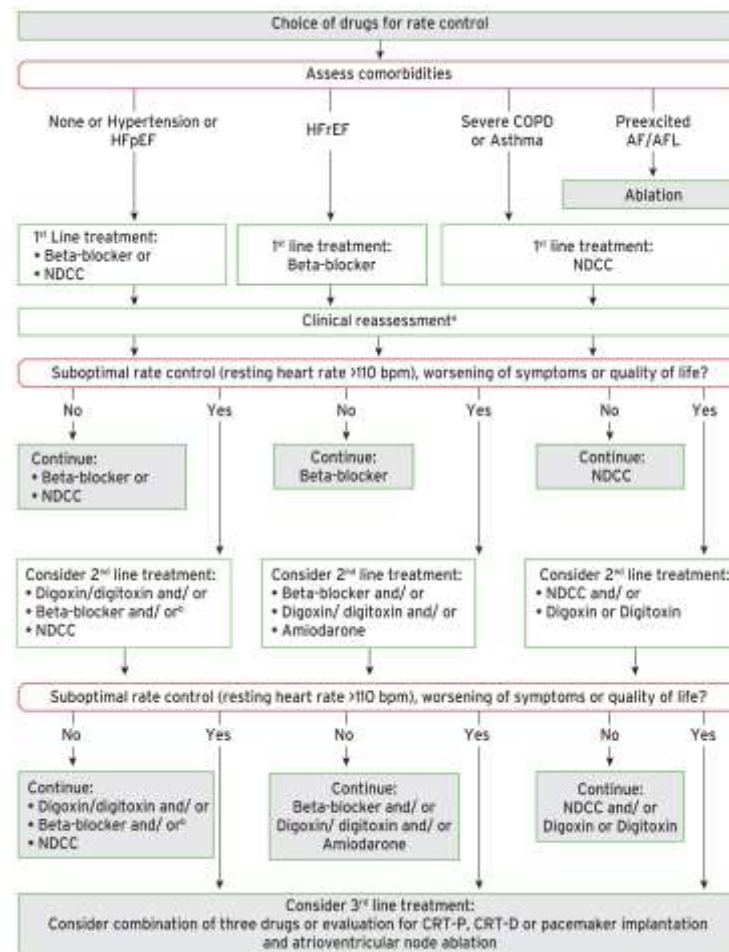


Figure 16-5: Choice of rate control drugs. A) Clinical reassessment should be focused on evaluation of resting heart rate, AF/AFL-related symptoms and quality of life. **B)** Careful institution of beta-blocker and NDCC, 24-hour Holter to check for bradycardia. **Source:** 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

| Table 16-11: ESC Recommendations for ventricular rate control in patients with AF: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF \geq 40%.</i> | I | B |
| <i>Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF < 40%.</i> | I | B |
| <i>Combination therapy comprising different rate controlling drugs ⁽¹⁾ should be considered if a single drug does not achieve the target heart rate.</i> | IIa | B |
| <i>A resting heart rate of < 110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy.</i> | IIa | B |
| <i>AV node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, and not eligible for rhythm control by LA ablation, accepting that these patients will become pacemaker dependent.</i> | IIa | B |
| <i>In patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate.</i> | IIb | B |

- **Rhythm control:**

- The 'rhythm control strategy' refers to attempts to restore and maintain sinus rhythm, and may engage a combination of treatment approaches, including cardioversion, antiarrhythmic medication, and catheter ablation, along with an adequate rate control, anticoagulation therapy.
- In old trials, long-term rhythm control, as compared with rate control, did not reduce mortality, stroke rate, or HF hospitalizations in patients at high risk of stroke or AF recurrences (AFFIRM and RACE trials), and in stable HF patients with EF

(1) Combining beta-blocker with verapamil or diltiazem should be performed with careful monitoring of heart rate by 24-h ECG to check for bradycardia.

< 35% (AF-CHF trial). This failure of rhythm control was partly related to the withdrawal of anticoagulation, the marginal efficacy of antiarrhythmic drugs, and AADs toxicity.

- Conversely, modern trials have shown that a rhythm control strategy is superior in 2 settings: HF or early AF (≤ 1 year, symptomatic or not, paroxysmal or persistent); as long as a safer and more effective rhythm control regimen is used, focused on AF ablation, over a background of anticoagulation and comprehensive risk factor management (CASTLE AF, CABANA).

- **Rhythm control options include:**

- 1. Cardioversion:**

- A. Electrical cardioversion
 - B. Antiarrhythmic drugs

- 2. Longterm rhythm control:**

- A. Catheter ablation
 - B. Surgical ablation
 - C. Longterm Antiarrhythmic drugs.

| Table 16-12: ESC Recommendations for rhythm control: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF. | I | A |

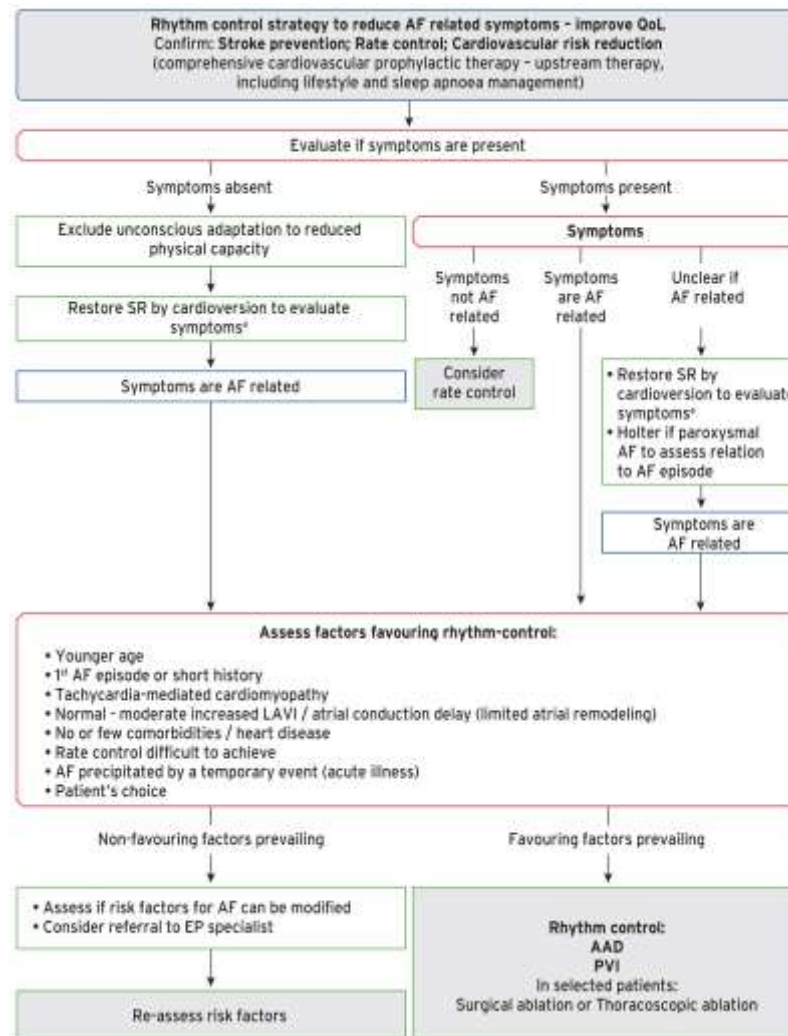


Figure 16-6: Rhythm control strategy. A) Consider cardioversion to confirm that the absence of symptoms is not due to unconscious adaptation to reduced physical and/or mental capacity. **Source:** 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

1. Cardioversion:

- In hemodynamically unstable AF patients, emergency cardioversion can achieve acute rhythm control and electrical cardioversion is the method of choice in this setting.
- In stable patients, either pharmacological cardioversion or electrical cardioversion can be attempted; pharmacological cardioversion is less effective but does not require sedation. Appropriate anticoagulation before and after cardioversion is crucial in order to avoid thromboembolic complications (the risk of stroke in the peri-cardioversion period is ~8%, reduced to < 0.5% with appropriate anticoagulation).

N.B: AF often spontaneously resolves by 24 hours, in ~60% of the cases (70% at 48 hours), even more so in the absence of heart disease. Thus, a 24-hour wait-and-see strategy is reasonable.

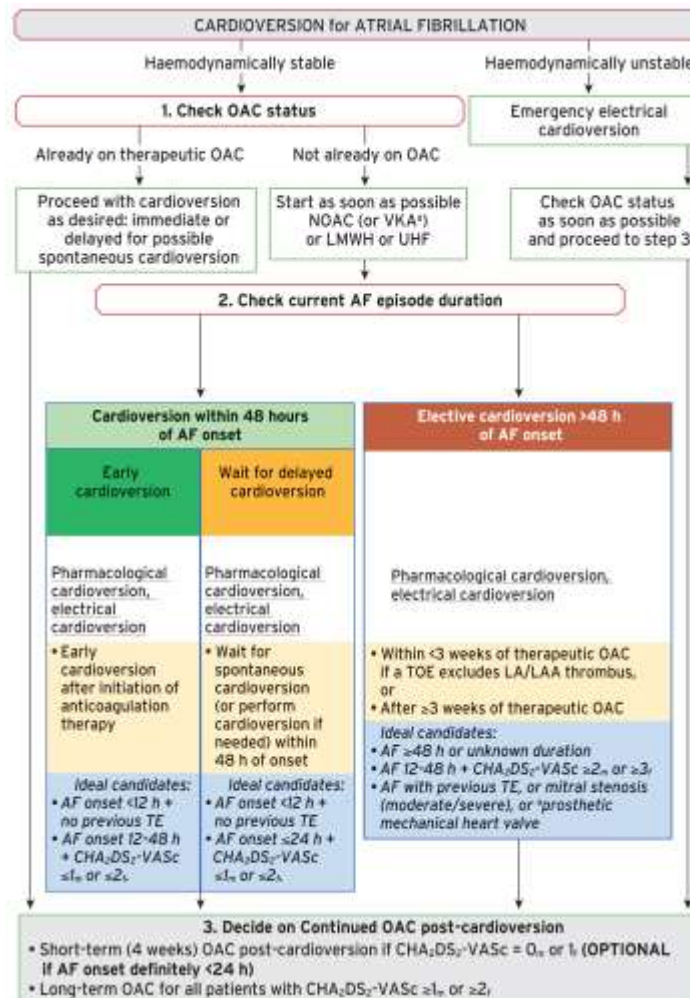


Figure 16-7: Flowchart for decision making on cardioversion of AF depending on clinical presentation, AF onset, oral anticoagulation intake, and risk factors for stroke. A) Alternatively, a VKA can be used, accounting for the time needed to achieve therapeutic anticoagulant effect. **Source:** 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

| Table 16-13: ESC Recommendations for cardioversion: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| AF in hemodynamically unstable patients: | | |
| <i>Emergency electrical cardioversion is recommended in AF patients with acute or worsening hemodynamic instability.</i> | I | B |
| <i>In AF patients with hemodynamic instability, amiodarone may be considered for acute control of heart rate.</i> | IIb | B |
| AF in hemodynamically stable patients: | | |
| <i>Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent AF as part of rhythm control therapy.</i> | I | B |
| <i>Pharmacological cardioversion of AF is indicated only in a hemodynamically stable patient, after consideration of the thromboembolic risk.</i> | I | B |
| <i>For pharmacological cardioversion of recent onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended.</i> | I | A |
| <i>Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation.</i> | I | A |
| <i>In selected patients with infrequent and recent onset AF and no significant structural or ischemic heart disease, a single self-administered oral dose of flecainide or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>Pre-treatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to facilitate the success of electrical cardioversion ⁽¹⁾.</i> | Ila | B |
| <i>For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (> 500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.</i> | III | C |
| Stroke risk management: | | |
| <i>In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety to warfarin.</i> | I | A |
| <i>For cardioversion of AF/AFL, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.</i> | I | B |
| <i>TOE is recommended to exclude cardiac thrombus as an alternative to 3-week pre procedural anticoagulation when early cardioversion is planned.</i> | I | B |
| <i>In patients at risk of stroke, it is recommended that OAC therapy is continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion, the apparent maintenance of sinus rhythm, or characterization of AF as a 'first-diagnosed episode'.</i> | I | B |
| <i>When thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks before cardioversion of AF.</i> | I | B |
| <i>It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.</i> | I | C |
| <i>Effective anticoagulation should be initiated as soon as possible before every cardioversion of AF or AFL.</i> | Ila | B |

(1) Antiarrhythmic drugs reduce immediate recurrence but do not help with DCCV failure, as most of them actually increase the atrial defibrillation threshold (except ibutilide, sotalol and dronedarone).

| | | |
|--|------------|----------|
| <i>Early cardioversion can be performed without TOE in patients with an AF duration of < 48 h.</i> | Ila | B |
| <i>In patients with AF duration of > 24 h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks ⁽¹⁾, even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors).</i> | Ila | B |
| <i>When thrombus is identified on TOE, a repeat TOE to ensure thrombus resolution should be considered before cardioversion.</i> | Ila | C |
| <i>In patients with a definite duration of AF ≤ 24 h and a very low stroke risk (CHA₂DS₂-VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted.</i> | Ilb | C |

(1) AF conversion to sinus rhythm is followed by a few weeks of atrial hypocontractility, during which a thrombus may form then embolize once the atria fully recover their contractility.

| Table 16-14: Antiarrhythmic drugs used for restoration of sinus rhythm: | | | |
|---|--|---|--|
| Administration route | Initial dose | Further dosing | Acute success rate and expected time to sinus rhythm |
| Flecainide Oral, I.V | 200-300 mg 2 mg/kg over 10 min. | - | Overall: 59-78% (51% at 3 hrs, 72% at 8 hrs) |
| Propafenone Oral, I.V | 450-600 mg 1.5-2 mg/kg over 10 min. | - | - Oral: 45-55% at 3 hrs, 69-78% at 8 hrs. - IV: 43-89% Up to 6 hrs |
| Contraindications/precautions/comments: <ul style="list-style-type: none"> - Should not be used in ischemic heart disease and/or significant structural heart disease. - May induce hypotension, AFL with 1:1 conduction (in 3.5-5 % of patients) - Flecainide may induce mild QRS complex widening - Don't use for pharmacological cardioversion of AFL. | | | |
| Vernakalant I.V | 3 mg/kg over 10 min. | 2 mg/kg over 10 min. (10-15 min. after the initial dose) | < 1 hr. (50% conversion within 10 min.) |
| Contraindications/precautions/comments: <ul style="list-style-type: none"> - Should not be used in patients with arterial hypotension (SBP < 100 mmHg), recent ACS (within 1 month), NYHA III or IV HF, prolonged QT, or severe AS. - May cause arterial hypotension, QT prolongation, QRS widening or non-sustained VT. | | | |
| Amiodarone I.V | 5-7 mg/Kg over 1-2 h | 50 mg/hr | 44% 8-12 h to several days |

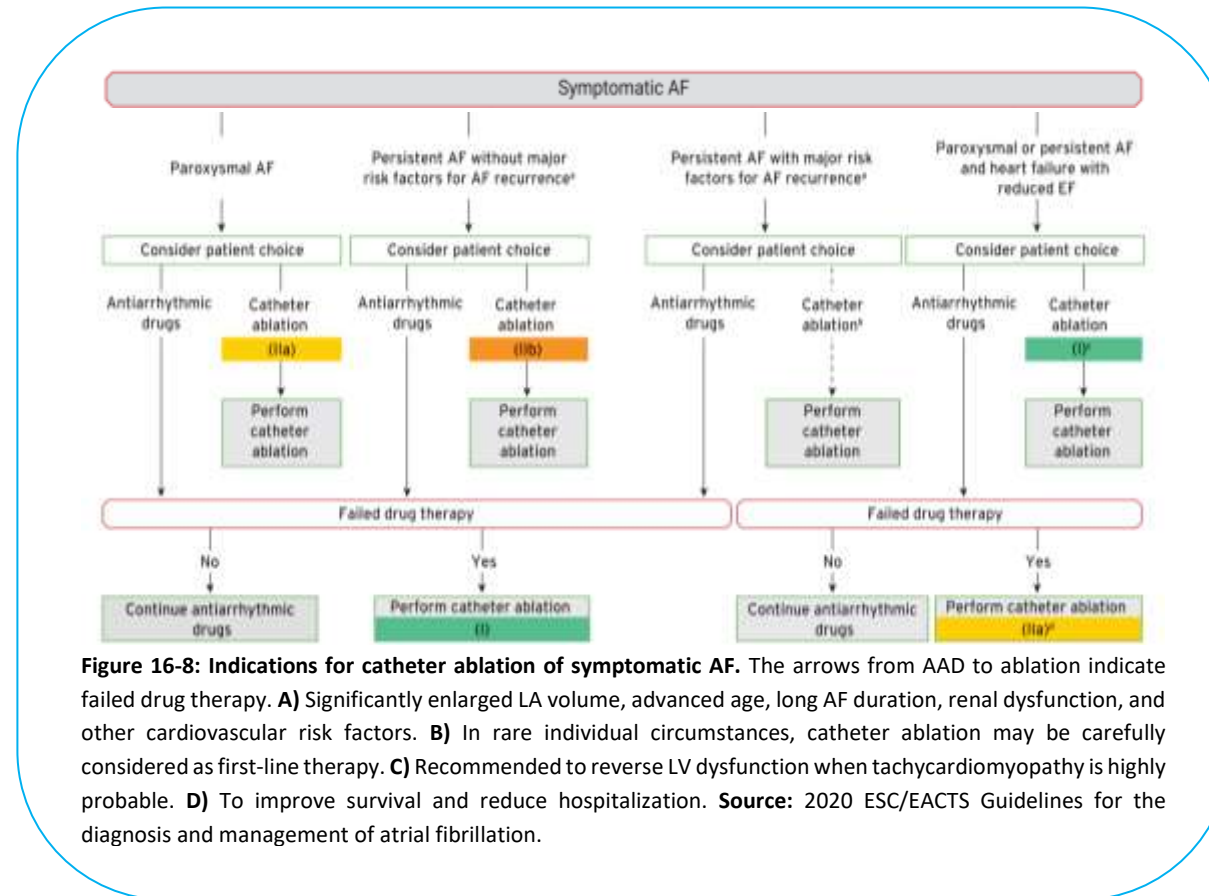
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|--|---|---|--------------------------------------|
| | | (Max. 1.2 g for 24 hrs) | |
| Contraindications/precautions/comments: <ul style="list-style-type: none"> - May cause phlebitis (Use a large peripheral vein, avoid I.V administration > 24 h and use preferably volumetric pump) - May cause hypotension, bradycardia/AV block, QT prolongation. | | | |
| Ibutilide I.V | 1 mg over 10 min. 0.01 mg/kg if BW < 60 kg | 1 mg over 10 min (10-20 min. after initial dose) | 31-51% (AF) 63-73% (AFL) ≈1 hr |
| Contraindications/precautions/comments: <ul style="list-style-type: none"> - Effective for cardioversion of AFL. - Should not be used in patients with prolonged QT, severe LVH or low LVEF. - Should be used in the setting of a CCU as it may cause QT prolongation, polymorphic VT (torsade de pointes). - ECG monitoring for at least 4 hrs after administration to detect a proarrhythmic event. | | | |

2. Long-term Rhythm control:

▪ Catheter ablation:

- AF catheter ablation is a well-established treatment for the prevention of AF recurrences. Up to 90% of PACs that trigger AF originate from the pulmonary veins, while the rest originate from other foci, most commonly SVC and posterior LA wall, which shares the same embryonic origin as the pulmonary veins.
- The cornerstone of AF catheter ablation is the complete isolation of pulmonary veins by linear lesions around their antrum, either using point-by-point delivery of radiofrequency energy (“fire”), or a faster and simpler, one-step cryoballoon inflation across each pulmonary vein origin (“ice”).

- The success is highest in patients with paroxysmal AF, no or minimal heart disease, no or minimal left atrial enlargement, and no severe lung disease.
- **Indications:**



- Blanking (blinding) period is defined as a period of time post-ablation (mostly 3 months) during which any recurrence of AF, atrial flutter, or atrial tachycardia is not considered a failure of the procedure nor is it suggestive of long-term AF recurrence. The underlying mechanisms of early recurrence during the blinding period is modulated by procedure-induced

pathophysiological changes, such as necrosis, ischemia, edema, inflammation, autonomic nervous disbalance, and tissue repair including scar formation. Some of these factors are proarrhythmic and diminish with time leading to a delayed cure, whereas others are antiarrhythmic and wane leading to a delayed therapy failure.

○ **Complications:**

- Pulmonary vein stenosis is seen in < 1% of patients after AF ablation, and is diagnosed by cardiac CT.
- Stiff LA syndrome, caused by LA fibrosis, may be seen after aggressive LA ablation.

Both entities may cause new HF or worsening of HF after AF ablation; both are characterized by a discrepancy between LVEDP and a much higher PCWP, in the absence of MS.

- Phrenic nerve injury may be seen with cryoballoon ablation (3%), but is rarely permanent (<0.5%)
- Recurrence of AF: Several AF risk factors may contribute to the development of LA substrates, predisposing to a higher recurrence rate. Aggressive control of modifiable risk factors may reduce recurrence rate.



Figure 16-9: Risk factors for AF recurrence after AF ablation. Source: 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

○ Follow-up after AF ablation:

Table 16-15: Key issues in follow-up after AF catheter ablation

Follow-up monitoring:

- *Patients should be first reviewed at a minimum of 3 months and annually thereafter.*
- *Monitoring may be performed with intermittent ECG, Holter, Patch recordings, external or implanted loop recorder, or smart phone monitor (although the latter has not been validated for such use).*
- *Useful to assess procedural success and correlate symptom status with rhythm.*
- *Recurrences beyond the first month post-ablation are generally predictive of late recurrences, but recurrent symptoms may be due to ectopic beats or other non-sustained arrhythmia; conversely the presence of asymptomatic AF after ablation is well described.*

Management of antiarrhythmic medication and treatment of AF recurrences:

- a. *Continuing AAD treatment for 6 weeks to 3 months may reduce early AF recurrences, rehospitalizations and cardioversions during this period.*
- b. *Clinical practice regarding routine AAD treatment after ablation varies and there is no convincing evidence that such treatment is routinely needed. Subsequently, AADs may be weaned, ceased, or continued according to symptoms and rhythm status. Recent findings suggest that in AAD-treated patients remaining free of AF at the end of the blanking period ⁽¹⁾, AAD continuation beyond the blanking period reduces arrhythmia recurrences.*

(1) *The blanking (blinding) period is defined as a period of time post-ablation (mostly 3 months) during which any recurrence of AF, atrial flutter, or atrial tachycardia is not considered a failure of the procedure nor is it suggestive of long-term AF recurrence. The underlying mechanisms of early recurrence during the blinding*

Management of anticoagulation therapy:

- In general, OAC therapy is continued for 2 months following ablation in all patients.
- Beyond this time, a decision to continue OAC is determined primarily by the presence of CHA₂DS₂-VASc stroke risk factors rather than the rhythm status.

Table 16-16: ESC Recommendations for catheter ablation of AF:

| Recommendations | Class | Level |
|--|--------------|--------------|
| General recommendations: | | |
| <i>For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.</i> | I | B |
| <i>Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI.</i> | IIa | B |
| AF catheter ablation after failure of drug therapy: | | |
| <i>AF catheter ablation for PVI is recommended for rhythm control after failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with:</i> | | |
| - Paroxysmal AF, or | I | A |
| - Persistent AF without major risk factors for AF recurrence, or | I | A |
| - Persistent AF with major risk factors for AF recurrence | I | B |

period is modulated by procedure-induced pathophysiological changes, such as necrosis, ischemia, edema, inflammation, autonomic nervous disbalance, and tissue repair including scar formation. Some of these factors are proarrhythmic and diminish with time leading to a delayed cure, whereas others are antiarrhythmic and wane leading to a delayed therapy failure.

| | | |
|--|------------|----------|
| <i>AF catheter ablation for PVI should be considered for rhythm control after failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.</i> | Ila | B |
| First-line therapy: | | |
| <i>AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic:</i> | | |
| <i>- Paroxysmal AF episodes, or</i> | Ila | B |
| <i>- Persistent AF without major risk factors for AF recurrence.</i> | Ilb | C |
| <i>as an alternative to AAD class I or III, considering patient choice, benefit, and risk.</i> | | |
| AF catheter ablation: | | |
| <i>- Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.</i> | I | B |
| <i>- Should be considered in selected AF patients with HFrEF to improve survival and reduce HF hospitalization.</i> | Ila | |
| <i>AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation.</i> | Ila | C |
| Techniques and technologies: | | |
| <i>Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.</i> | I | A |
| <i>If patient has history of CTI-dependent AFL or if typical AFL is induced at the time of AF ablation, delivery of a CTI lesion may be considered.</i> | Ilb | B |
| <i>Use of additional ablation lesions beyond PVI (low voltage areas, lines, fragmented activity, ectopic foci, rotors, and others) may be considered but is not well established.</i> | Ilb | B |

| | | |
|--|-----|---|
| Lifestyle modification and other strategies to improve outcomes of ablation: | | |
| <i>Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.</i> | I | B |
| <i>Strict control of risk factors and avoidance of triggers are recommended as part of a rhythm control strategy.</i> | I | B |
| Stroke risk management: | | |
| <i>In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and:</i> - Preferably, therapeutic OAC for at least 3 weeks before ablation, or - Alternatively, the use of TOE to exclude LA thrombus before ablation. | I | C |
| | Ila | C |
| <i>For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin or NOACs, performance of the ablation procedure without OAC interruption is recommended.</i> | I | A |
| <i>After AF catheter ablation, it is recommended that:</i> - Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation (as the injured atrial tissue may trigger clot formation). - Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. | I | C |

B. Surgical ablation of AF:

Maze procedure consists of creating lines around the pulmonary veins, +/- biatrial ablation lines. The use of radiofrequency energy rather than cutting and sewing allows a faster and less morbid procedure.

Ablation increases pump time by ~15 min and is indicated along with any cardiac surgery in a patient with persistent or symptomatic AF.

Surgical ablation is effective in controlling AF but is associated with a higher post-surgical requirement for pacemaker therapy vs no ablation (21.5% vs 8%).

Surgical ablation may also be done as a stand-alone thoracoscopic procedure in patients who failed catheter ablation (it is more effective [FAST trial]).

| Table 16-17: ESC Recommendations for surgical ablation of AF: | | |
|---|------------|----------|
| Recommendations | Class | Level |
| <i>Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (LA dilatation, years in AF, age, renal dysfunction, and other CV risk factors).</i> | Ila | A |
| <i>Thoracoscopic -including hybrid surgical ablation- procedures should be considered in patients who have symptomatic paroxysmal or persistent AF refractory to AAD therapy and have failed percutaneous AF ablation, or with evident risk factors for catheter failure, to maintain long-term sinus rhythm. The decision must be supported by an experienced team of electrophysiologists and surgeons.</i> | Ila | B |
| <i>Thoracoscopic -including hybrid surgical ablation- procedures may be considered in patients with persistent AF with risk factors for recurrence, who remain symptomatic during AF despite at least one failed AAD and who prefer further rhythm control therapy.</i> | Ilb | C |
| Stroke risk management: | | |
| <i>Long-term OAC therapy is recommended in patients after AF surgery and appendage closure, based on the patient's thrombo-embolic risk assessed with the CHA₂DS₂-VASc score.</i> | I | C |

C. Long-term antiarrhythmic drug therapy:

The aim of AAD therapy is to improve AF-related symptoms. Hence, the decision to initiate long-term AAD therapy needs to balance symptom burden, possible adverse drug reactions, and patient preferences. The choice of the drugs to be used in the individual patient should be primarily guided by safety rather than efficacy considerations and is significantly influenced by patient's comorbidities.

| Table 16-18: Rules to initiate antiarrhythmic drugs for long-term rhythm control in AF: | |
|---|---|
| Consideration | Criteria |
| Indication for AAD | <ul style="list-style-type: none"> - <i>Is the patient symptomatic?</i> - <i>Are AF symptoms severe enough (EHRA class) to justify AAD use?</i> - <i>Are there associated conditions predicting poor tolerance of AF episodes?</i> |
| When to start AAD | <ul style="list-style-type: none"> - <i>Usually not for the first episode, but it may enhance efficacy of cardioversion.</i> |
| How to choose among AADs | <ul style="list-style-type: none"> ○ <i>Minimize proarrhythmic risk and organ toxicity.</i> ○ <i>Evaluate for:</i> <ul style="list-style-type: none"> - <i>basal ECG abnormalities (QRS duration, PR, QTc) and possible interference with AAD</i> - <i>impact on LV function</i> - <i>important pharmacokinetic and pharmacodynamics interactions (i.e. antithrombotic drugs).</i> ○ <i>Risk factors for proarrhythmia may be dynamic and change over time</i> |
| How to minimize proarrhythmic risk | <ul style="list-style-type: none"> - <i>Evaluate ECG after the treatment.</i> - <i>Evaluate periodically for organ toxicity (amiodarone)</i> - <i>Long-term Holter monitoring and exercise test in selected cases</i> - <i>Avoid AAD combinations</i> |
| How to verify efficacy | <ul style="list-style-type: none"> - <i>Estimate AF burden under therapy (ask patient for noting episodes)</i> - <i>If the patient is already on AAD and it was effective but was stopped because of intolerance, choose preferably from the same class.</i> |

| | |
|--|---|
| Adjuvant interventions and hybrid therapy | <ul style="list-style-type: none"> - In patients with atrioventricular conduction abnormalities and/or sinus node dysfunction, pacemaker implantation should be considered if AAD therapy is deemed necessary. - Short-term AAD therapy could prevent early recurrences after AF ablation |
|--|---|

Table 16-19: ESC Recommendations for long-term antiarrhythmic drugs:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.</i> | I | A |
| <i>Dronedarone is recommended for long-term rhythm control in AF patients with:</i> <ul style="list-style-type: none"> - Normal or mildly impaired (but stable) LV function, or - HFpEF, ischaemic, or VHD. | I | A |
| <i>Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia.</i> | I | A |
| <i>In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.</i> | I | B |
| <i>In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.</i> | IIa | C |
| <i>Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT</i> | IIb | A |

interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided.

AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless antibradycardia pacing is provided.

| | |
|-----|---|
| | |
| III | C |

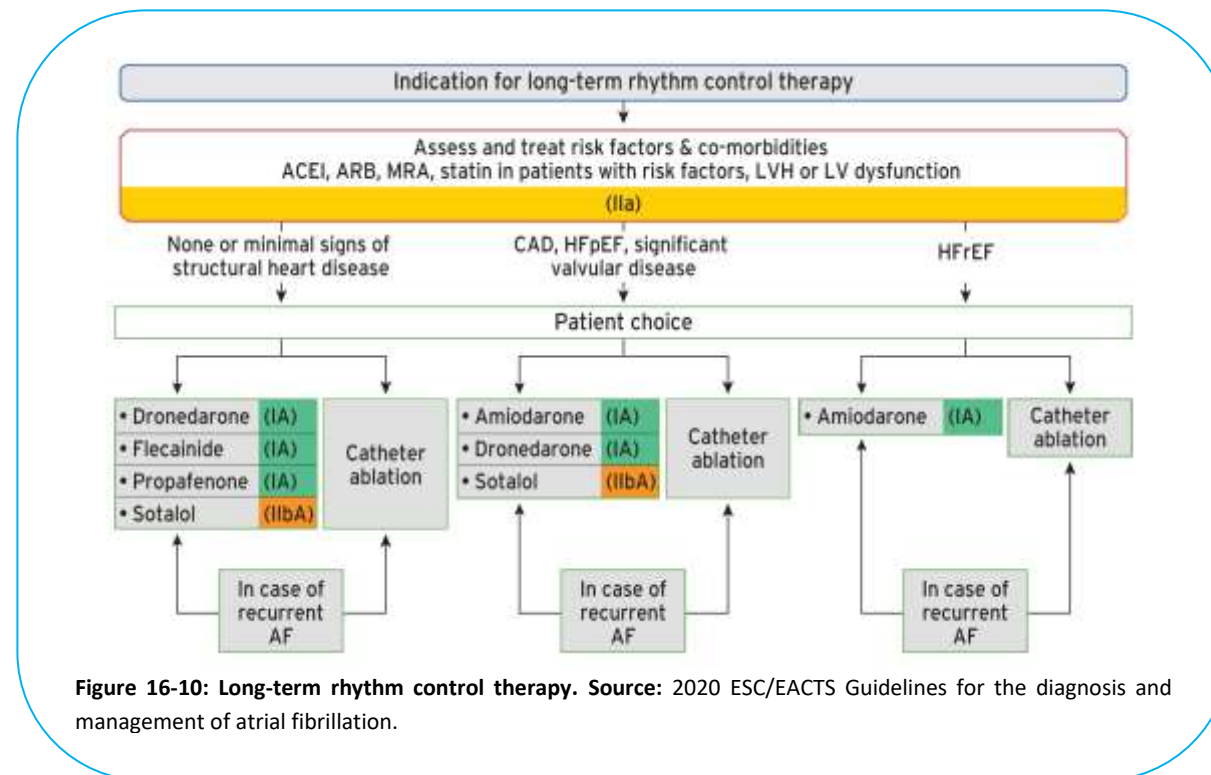


Table 16-20: Antiarrhythmic drugs used for oral long-term maintenance of sinus rhythm in AF patients:

| Drug/Dose | Contraindications/precautions/comments |
|---|---|
| Amiodarone 3 x 200 mg daily over 4 weeks, then 200 mg daily | <ul style="list-style-type: none"> - The most effective AAD - RCTs showed lower AF recurrence compared with sotalol and dronedarone - Also reduces ventricular rate (for 10 - 12 bpm), safe in patients with HF - Concomitant use with other QT-prolonging drugs with caution - Concomitant use with VKAs or digitalis (their dose should be reduced) - Increased risk of myopathy when used with statins - Requires regular surveillance for liver, lung, and thyroid toxicity - Has atrioventricular nodal-slowng properties, but should not be used as first intention for rate control. - QT prolongation is common but rarely associated with torsades de pointes (<0.5%) - Torsades de pointes occurs infrequently during treatment with amiodarone (the proarrhythmia caution requires QT-interval and TU wave monitoring) - Should be discontinued in case of excessive QT prolongation (>500 ms) - ECG at baseline, after 4 weeks - Contraindicated in manifest hyperthyroidism - Numerous and frequent extracardiac side-effects may warrant discontinuation of amiodarone, so making it a second-line treatment when other choices are possible. |
| Flecainide 100 - 200 mg b.i.d, or 200 mg once daily | <ul style="list-style-type: none"> - Effective in preventing recurrence of AF. - Should not be used in patients with CrCl <35 mL/min/1.73 m² and significant liver disease. - Both are contraindicated in patients with ischaemic heart disease or reduced LVEF. - Should be discontinued in case of QRS widening >25% above baseline and patients with LBBB or any other conduction block >120 ms |

| | |
|---|---|
| (flecainide slow release) | <ul style="list-style-type: none"> - Caution when sinoatrial/atrioventricular conduction disturbances present ⁽¹⁾ - CYP2D6 inhibitors increase concentration. - May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate. This risk can be reduced by concomitant administration of an atrioventricular nodal blocking drug such as a beta-blocker or NDCC. - In patients properly screened for propensity to proarrhythmias, both flecainide and propafenone are associated with a low proarrhythmic risk. - ECG at baseline, after 1 - 2 weeks |
| Propafenone 150 - 300 mg t.i.d | <ul style="list-style-type: none"> - Should not be used in patients with significant renal or liver disease, ischaemic heart disease, reduced LV systolic function, or asthma - Should be discontinued in case of QRS widening >25% above baseline and in patients LBBB and any other conduction block >120 ms - Caution when sinoatrial/atrioventricular conduction disturbances present - Increases concentration of warfarin/acenocoumarin and digoxin when used in combination. - May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate - ECG at baseline and after 1 - 2 weeks |
| Dronedaron 400 mg b.i.d. | <ul style="list-style-type: none"> - Less effective than amiodarone in rhythm control but has very few extracardiac side-effects. - Reduces cardiovascular hospitalizations and death in patients with paroxysmal or persistent AF or AFL and cardiovascular comorbidity. - Associated with increased mortality in patients with recent decompensated HF or permanent AF. - Dronedaron has the most solid safety data and may be a preferable first choice, however not indicated in patients with HF and permanent AF. |

(1) Caution is needed when using any AAD in patients with conduction-system disease (e.g. SA or AV node disease)

| | |
|---|--|
| | <ul style="list-style-type: none"> - Should not be used in NYHA class III or IV or unstable HF, in combination with QT-prolonging drugs or with strong CYP3A4 inhibitors (e.g. verapamil, diltiazem) and in patients with CrCl <30 mL/min. - Concomitant use with dabigatran is contraindicated - Combination with digoxin may significantly increase digoxin serum concentration. - When used with digitalis or beta-blockers their doses should be reduced - Should be discontinued in case of excessive QT prolongation (>500 ms or >60 ms increase) - A modest increase in serum creatinine is common and reflects drug induced reduction in CrCl rather than a decline in renal function. - Has atrioventricular nodal-slowng properties. - ECG at baseline and after 4 weeks |
| Sotalol 80 - 160 mg b.i.d. | <ul style="list-style-type: none"> - Only class III effects if dosing >160 mg daily - Considering its safety and efficacy and potential drug alternatives, sotalol should be used with a caution. - Should not be used in patients with HFrEF, significant LVH, prolonged QT, asthma, hypokalaemia, or CrCl <30 mL/min - Dose-related torsades de pointes may occur in >2% of patients. - Should be discontinued in case of excessive QT prolongation (>500 ms or >60 ms increase) - Should not be used if CrCl <50 mL/min - The potassium channel-blocking effect increases with increasing dose and, consequently, the risk of ventricular proarrhythmia (torsades de pointes) increases - Observational data and a recent meta-analysis revealed a correlation with an increased all-cause mortality, whereas a nationwide registry analysis and two RCTs found no evidence for increased safety concerns with sotalol. - ECG at baseline, after 1 day and after 1 - 2 weeks |

| | |
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| Disopyramide 100-400 mg t.i.d. (max. 800mg/24h) | <ul style="list-style-type: none"> - Associated with significantly increased mortality, and rarely used for rhythm control in AF. Should not be used in patients with a structural heart disease. Rarely used for rhythm control in AF patients, due to increased mortality and frequent intolerance to side effects - May be useful in 'vagal' AF occurring in athletes or during sleep. - Reduces LV outflow obstruction and symptoms in patients with HCM. |
|---|--|

▪ **'C' Cardiovascular risk factors and concomitant diseases:**

The 'C' component of the ABC pathway includes identification and management of concomitant diseases, cardiometabolic risk factors, and unhealthy lifestyle factors. Management of risk factors and cardiovascular disease complements stroke prevention and reduces AF burden and symptom severity.

For example, weight loss > 10% in patients with BMI > 27 kg/m² dramatically reduces the recurrence of AF. Weight loss, by itself, is almost as effective as antiarrhythmic drugs in preventing AF recurrence, and it allows interruption of antiarrhythmic drugs in many patients. Also, weight loss is synergistic with AF ablation and antiarrhythmic therapy.

Table 16-21: ESC Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|---------------------|---------------------|
| <i>Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.</i> | I | B |
| <i>Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.</i> | I | B |
| <i>Opportunistic screening for AF is recommended in hypertensive patients.</i> | I | B |
| <i>Opportunistic screening for AF should be considered in patients with OSA.</i> | IIa | C |
| <i>Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.</i> | I | B |
| <i>In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.</i> | IIa | B |
| <i>Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy.</i> | IIa | B |

| | | |
|---|------------|----------|
| <i>Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.</i> | IIa | C |
| <i>Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms.</i> | IIb | C |

The ABC pathway in specific clinical settings:

- **ACS, PCI, and CCS in patients with AF:** see chapter: Antithrombotic in IHD
- **Acute stroke or intracranial hemorrhage in patients with AF:**
 - **In TIA:** effective anticoagulation should be started as soon as possible.
 - **In ischemic stroke:**
 - Anticoagulation is postponed 3-6 days in small cerebral infarction, and 12 days in large cerebral infarction. It is reasonable to exclude hemorrhagic transformation by head CT before starting anticoagulation.
 - Long-term secondary stroke prevention: There is no evidence that the addition of aspirin to OAC or supratherapeutic INRs would improve outcomes in secondary stroke prevention. NOACs, compared with VKAs, were associated with better efficacy and safety in secondary stroke prevention.
 - **In Intracranial hemorrhage (ICH):** The optimal timing of anticoagulation after ICH is unknown, but should be reconsidered, at 4 weeks, in patients with very high thromboembolic risk whose bleeding risk factor has been treated (e.g., HTN that is now controlled, berry aneurysm that is coiled or clipped).
In AF patients at very high risk of recurrent ICH, LAA occlusion may be considered. NOACs should be preferred in NOAC-eligible ICH survivors with AF although there is no RCT to prove this.

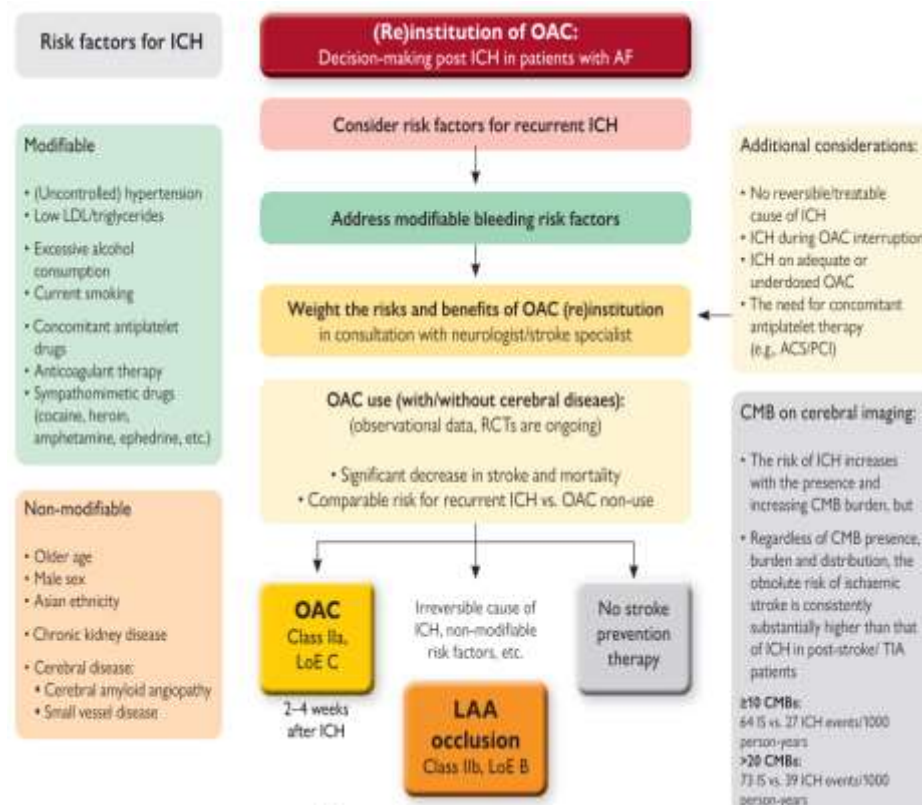


Figure 16-11: (Re-) initiation of anticoagulation post-intracranial bleeding. Source: 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

Table 16-22: ESC Recommendations for the management of stroke in patients with AF:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| AF in patients with cryptogenic stroke (stroke of uncertain aetiology): | | |

| | | |
|---|------------|----------|
| <i>In patients with acute ischemic stroke or TIA and without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible.</i> | I | B |
| <i>In selected ⁽¹⁾ stroke patients without previously known AF, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF.</i> | Ila | B |
| AF and acute ischemic stroke or TIA: | | |
| <i>In AF patients with ischemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients.</i> | I | A |
| <i>In AF patients presenting with acute ischemic stroke, very early anticoagulation (< 48 h) using UFH, LMWH, or VKAs is not recommended ⁽²⁾.</i> | III | B |
| AF patients after intracranial hemorrhage: | | |
| <i>In AF patients at high risk of ischemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: - A trauma-related ICH</i> | Ila | C |

(1) Not all stroke patients would benefit from prolonged ECG monitoring; those deemed at risk of developing AF (e.g. elderly, with cardiovascular risk factors or comorbidities, indices of LA remodelling, high C2HEST score, etc.) or those with cryptogenic stroke and stroke characteristics suggestive of an embolic stroke should be scheduled for prolonged ECG monitoring.

(2) using UFH, LMWH, or VKAs < 48 h after acute ischemic stroke was associated with an increased risk of symptomatic ICH, without significant reduction in recurrent ischemic stroke.

- Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral hemorrhage), after careful consideration of risks and benefits⁽¹⁾.

• **Active bleeding on anticoagulant therapy:**

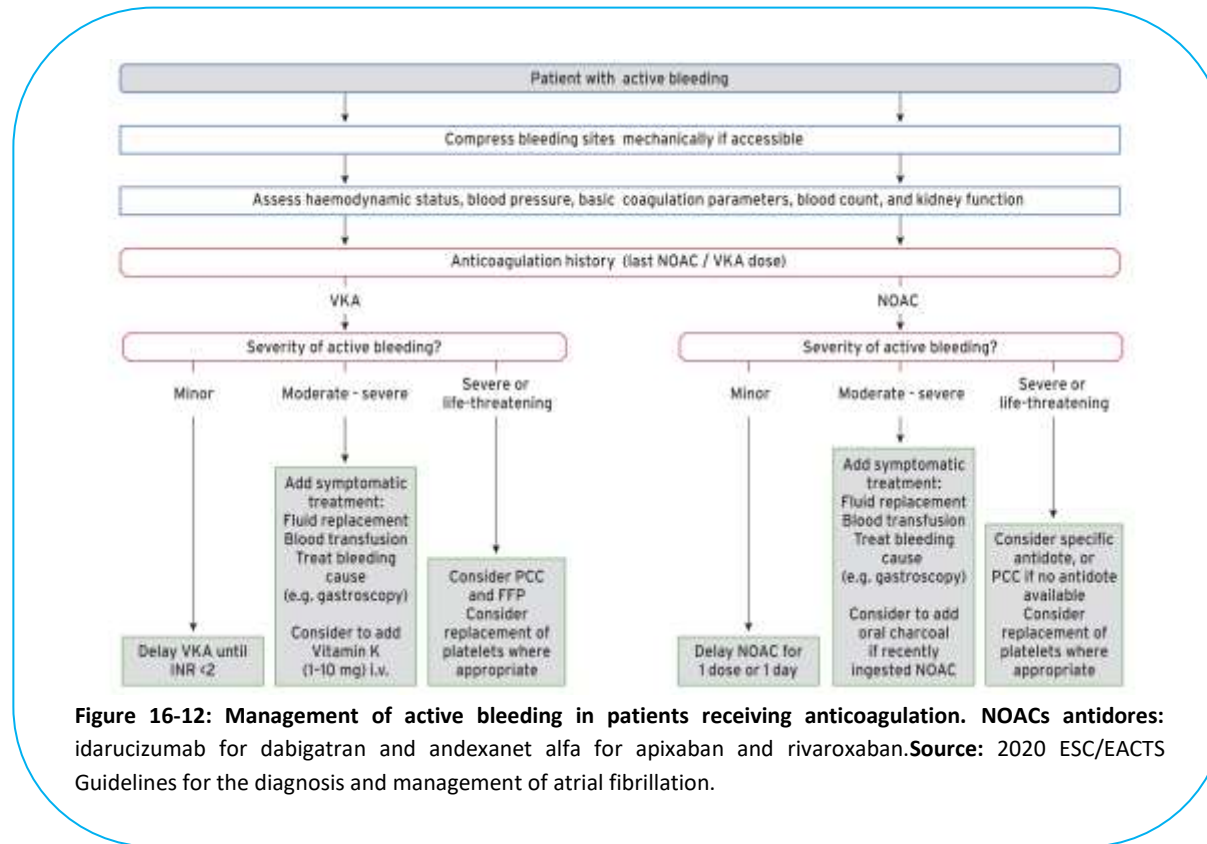


Table 16-23: ESC Recommendations for the management of active bleeding on OAC:

| Recommendations | Class | Level |
|-----------------|-------|-------|
|-----------------|-------|-------|

(1) A more favourable net benefit is likely with deep ICH or without neuroimaging evidence of cerebral amyloid angiopathy or microbleeds.

| | | |
|---|------------|----------|
| <p><i>In an AF patient with severe active bleeding, it is recommended to:</i></p> <ul style="list-style-type: none"> <i>- Interrupt OAC until the cause of bleeding is identified and active bleeding is resolved; and</i> <i>- Promptly perform specific diagnostic and treatment interventions to identify and manage the cause(s) and source(s) of bleeding.</i> | I | C |
| <p><i>Four-factor prothrombin complex concentrates should be considered in AF patients on VKA who develop a severe bleeding complication.</i></p> | Ila | C |

▪ **Atrial fibrillation and congenital heart disease:**

| Table 16-24: ESC Recommendations for the management of AF in patients with congenital heart diseases: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <ul style="list-style-type: none"> <i>- Oral anticoagulation should be considered in all adult patients with intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle and a history of AF, AFL, or intra-atrial re-entrant tachycardia.</i> <i>- In patients with AF and other congenital heart diseases, anticoagulation should be considered in the presence of one or more non-sex stroke risk factor(s).</i> | Ila | C |
| <p><i>Surgery for AF should be considered in patients:</i></p> <ul style="list-style-type: none"> <i>- Who need surgical closure of an atrial septal defect and who have a history of symptomatic atrial arrhythmia (atrial ablation should be considered at the time of surgical closure).</i> <i>- Cox maze surgery should be considered in patients with symptomatic AF and an indication for corrective repair of congenital heart defects. The surgery should be done in experienced centres.</i> | Ila | C |

| | | |
|---|------------|----------|
| <i>AF catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres.</i> | IIb | C |
| <i>In patients with congenital heart disease, TOE may be considered together with 3-week anticoagulation therapy before cardioversion.</i> | IIb | C |

▪ **Atrial fibrillation during pregnancy:**

| Table 16-25: ESC Recommendations for the management of AF during pregnancy: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Acute management: | | |
| <i>Immediate electrical cardioversion ⁽¹⁾ is recommended in case of hemodynamic instability or pre-excited AF.</i> | I | C |
| <i>In pregnant women with HCM, cardioversion should be considered for persistent AF.</i> | IIa | C |
| <i>Ibutilide or flecainide i.v. may be considered for termination of AF in stable patients with structurally normal hearts.</i> | IIb | C |
| Long-term management (oral administration of drugs) | | |
| <i>Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF.</i> | I | C |
| <i>Beta-selective blockers are recommended for rate control in AF ⁽²⁾</i> | I | C |
| <i>Flecainide, propafenone, ⁽³⁾ or sotalol ⁽⁴⁾ should be considered to prevent AF if AV nodal-blocking drugs fail.</i> | IIa | C |

(1) Cardioversion of AF should generally be preceded by anticoagulation.

(2) Atenolol has been associated with higher rates of foetal growth retardation and is not recommended.

(3) Flecainide and propafenone should be combined with AV nodal blocking drugs, but structural heart disease, reduced LV function, and bundle branch block should be excluded.

(4) Class III drugs should not be used in prolonged QTc

Digoxin or verapamil ⁽¹⁾ should be considered for rate control if beta-blockers fail

Ila

C

▪ **Postoperative atrial fibrillation:**

Postoperative AF (defined as new-onset AF in the immediate postoperative period) is a clinically relevant problem, occurring in 20 - 50% of patients after cardiac surgery (more so with valvular surgery, older age, HF, history of AF), 10 - 30% after noncardiac thoracic surgery, and in 5 - 10% after vascular or large colorectal surgery, with peak incidence between postoperative day 2 and 4. It is usually related to catecholamines and to the pericardial and generalized inflammation.

Many episodes of postoperative AF are self-terminating and some are asymptomatic, but postoperative AF has been associated with a four- to five-fold risk of recurrent AF in the next 5 years. It has also been shown to be a risk factor for stroke, MI, and death compared with non-postoperative AF patients.

(1) AV nodal-blocking drugs should not be used in patients with preexcitation on resting ECG or pre-excited AF.

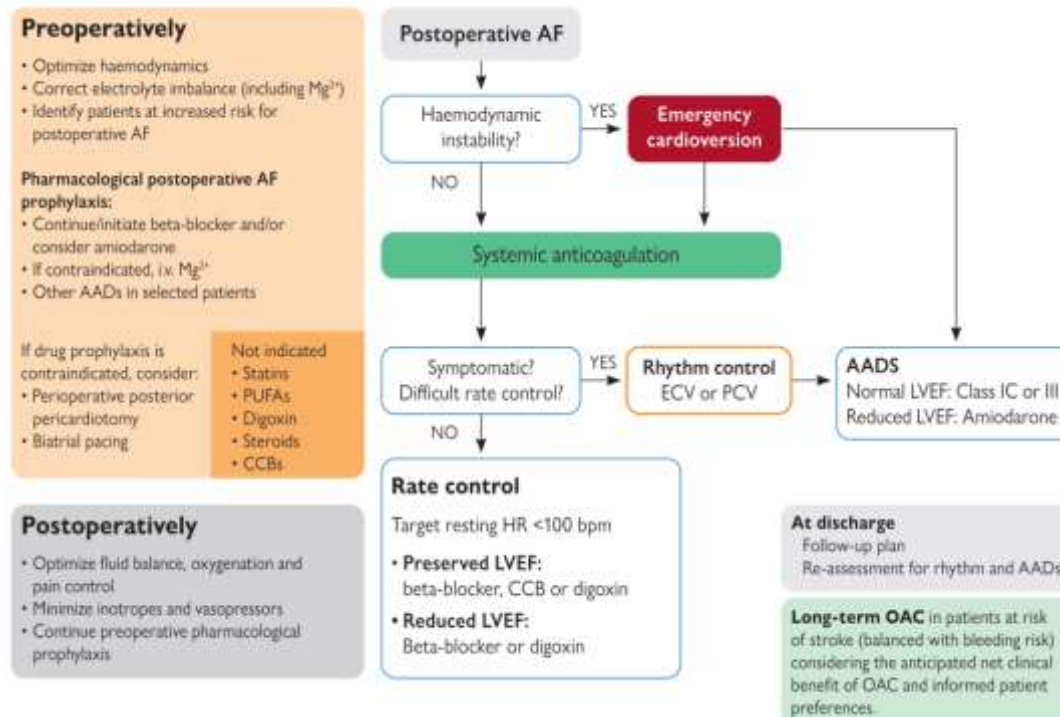


Figure 16-13: Management of postoperative AF. Source: 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation.

Table 16-26: ESC Recommendations for postoperative AF:

| Recommendations | Class | Level |
|--|-------|-------|
| Perioperative amiodarone or beta blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery. | I | A |
| Long-term OAC therapy to prevent thromboembolic events - should be considered in patients at risk for stroke with postoperative AF after non-cardiac surgery, | IIa | B |

| | | |
|--|-----|---|
| - may be considered in patients at risk for stroke with postoperative AF after cardiac surgery considering the anticipated net clinical benefit of OAC therapy and informed patient preferences. | IIb | B |
| Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery. | III | B |

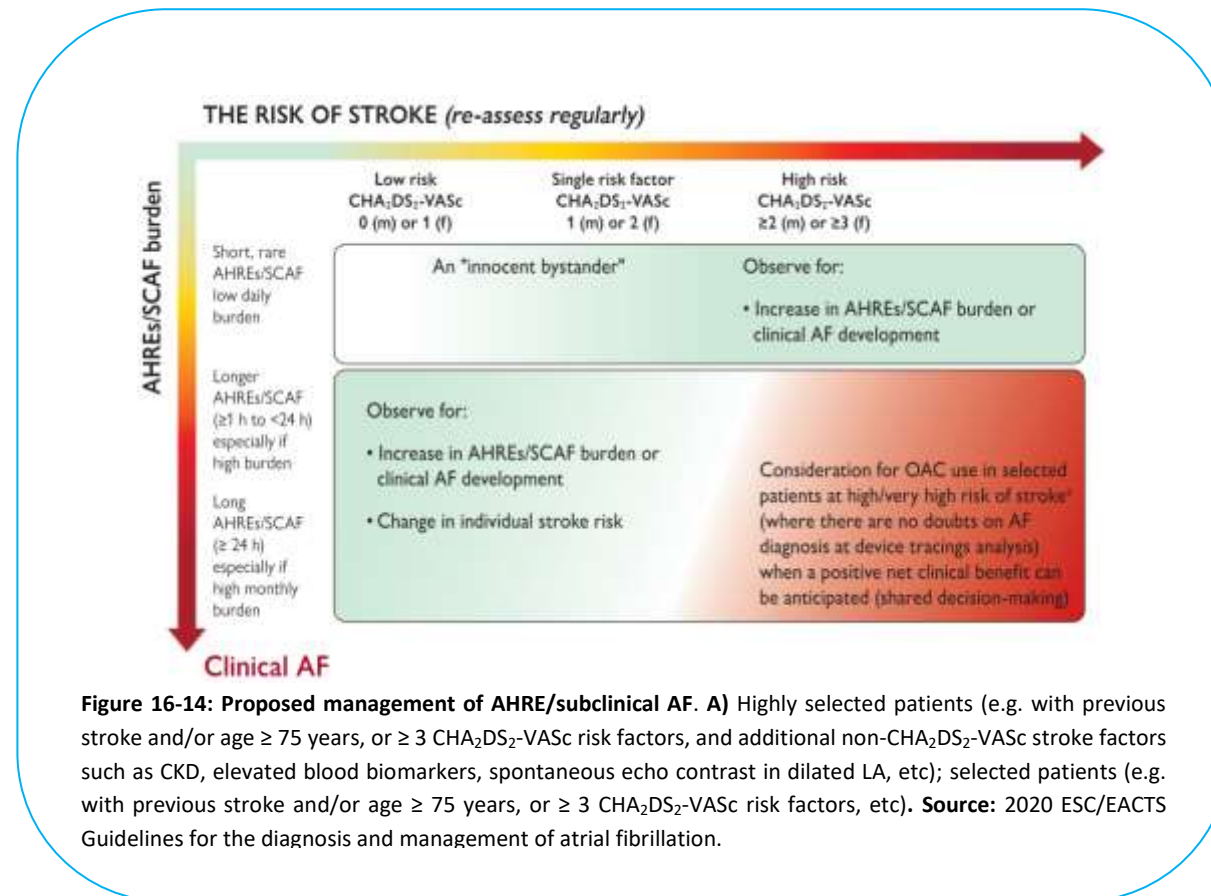
Atrial high-rate episodes/subclinical AF (SCAF):

Various implanted devices and wearable monitors allow detection of atrial high-rate episodes (AHRE)/subclinical AF. With increasing availability of such devices, proper use of specific terms is crucial to avoid misunderstanding, misclassification and inappropriate management. Although not completely identical, the terms AHRE and subclinical AF are often used interchangeably.

- **Atrial high-rate episode (AHRE)** - events fulfilling programmed or specified criteria for AHRE (atrial rate ≥ 175 bpm, for ≥ 5 min ⁽¹⁾) that are detected by cardiac implantable electronic device (CIEDs) with an atrial lead allowing automated continuous monitoring of atrial rhythm and tracings storage. CIED-recorded AHRE need to be visually inspected because some AHRE may be electrical artefacts/false positives.
- **Subclinical AF (SCAF):**
 - **Definition:** SCAF is defined as atrial high-rate episodes ≥ 5 min detected by cardiac monitoring devices -whether intracardiac (e.g., pacemakers), implantable (e.g., loop recorders), or wearable (e.g., smart watches)- confirmed to be AF, atrial flutter, or atrial tachycardia in absence of correlating symptoms.
 - **Incidence:** The incidence of AHRE/subclinical AF in patients with a pacemaker/ implanted device is 30-70%, but it may be lower in the general population.

(1) The reported duration refers to either the longest single episode or, more commonly, total duration of AHRE/subclinical AF during the specified monitoring period.

- **Duration:** Very short episodes ($\leq 10 - 20$ s/day) are considered clinically irrelevant, as they are not significantly associated with longer episodes or an increased risk of stroke or systemic embolism. However, longer episodes of AHRE/subclinical AF (minimum of 5 - 6 min) are associated with an increased risk of clinical AF, ischaemic stroke, major adverse CV events, and CV death (ASSERT study).
- Apart from AF duration, SCAF-related stroke risk appears to be influenced by traditional risk factors, including hypertension, DM, and ischemic cardiomyopathy. ASSERT showed an absolute increased stroke risk with an increasing CHADS2 score.
- **Predictors:** patients with SCAF appear to be older, more likely to have higher diastolic blood pressure, and a history of heart failure. It is more common among patients with a pacemaker indicated for sinus node dysfunction who had a high percentage of RV pacing.
- **Management:** Whereas available evidence is insufficient to justify routine OAC use in patients with AHRE/subclinical AF, modifiable stroke risk factors should be identified and managed in each patient. In selected patients with longer duration of AHRE/subclinical AF (≥ 24 hrs) and estimated high individual risk of stroke, the use of OAC may be considered. Overall, the absolute risk of stroke associated with AHRE/subclinical AF may be lower than with clinical AF, and the temporal dissociation from acute stroke suggests that AHRE/subclinical AF may represent a marker rather than a risk factor for stroke (a marker for left atrial fibrosis or myopathy).



| Table 16-27: ESC Recommendations for management of patients with AHRE: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <p><i>In patients with AHRE/subclinical AF detected by CIED or insertable cardiac monitor, it is recommended to conduct:</i></p> <ul style="list-style-type: none"> - <i>Complete cardiovascular evaluation with ECG recording, clinical risk factors/comorbidity evaluation, and thrombo-embolic risk assessment using the CHA₂DS₂-VASc score.</i> | I | B |

- Continued patient follow-up and monitoring (preferably with the support of remote monitoring) to detect progression to clinical AF, monitor the AHRE/subclinical AF burden (especially transition to ≥ 24 h), and detect changes in underlying clinical conditions.



Important trials in Atrial Fibrillation:

| Table 16-28: Clinical trials of Atrial Fibrillations: | |
|---|--|
| Trial (date) | Summary |
| Risk Factors: | |
| ALCOHOL-AF (2019) | <p>Aim: To evaluate abstinence from alcohol compared with usual consumption among patients with AF and moderate alcohol consumption.</p> <p>Study: 140 adults who consumed ≥ 10 standard drinks per week (with 1 standard drink containing approximately 12 g of pure alcohol) and who had paroxysmal or persistent AF in sinus rhythm at baseline were randomly assigned to either abstain from alcohol or continue their usual alcohol consumption. Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with atrial fibrillation.</p> |
| Screening of AF: | |
| EMBRACE (2014) | <p>Aim: To compare 30-day ECG monitoring with 24-h Holter monitoring in detection of AF in patients following cryptogenic stroke.</p> <p>Study: 572 patients ≥ 55 years of age, without known AF, who had had a cryptogenic ischemic stroke or TIA within the previous 6 months were randomly assigned to undergo additional noninvasive ambulatory ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a 24-hour monitor (control group). Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of AF by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the short-duration ECG monitoring.</p> |
| Anticoagulation: | |
| OAC vs placebo or Antiplatelet: | |
| AFASAK (1989) | <p>Aim: To assess whether anticoagulation therapy with warfarin could reduce the incidence of thromboembolism in patients with chronic AF</p> |

| | |
|----------------------|--|
| | <p>Study: 1007 outpatients with chronic non-rheumatic AF were randomly assigned to receive anticoagulation with warfarin openly, or to receive aspirin 75 mg once daily, or placebo. Each patient was followed up for 2 years or until termination of the trial. The primary endpoint was a thromboembolic complication (stroke, transient cerebral ischaemic attack, or embolic complications to the viscera and extremities). The incidence of thromboembolic complications and vascular mortality were significantly lower in the warfarin group than in the aspirin and placebo groups, which did not differ significantly. Thus, anticoagulation therapy with warfarin can be recommended to prevent thromboembolic complications in patients with chronic non-rheumatic AF.</p> |
| BAATAF (1990) | <p>Aim: To assess the effect of low-dose warfarin (target prothrombin-time ratio, 1.2 to 1.5) in patients with nonrheumatic AF</p> <p>Study: 420 patients with nonrheumatic AF were randomly assigned to receive low-dose warfarin therapy (target prothrombin-time ratio, 1.2 to 1.5) or placebo. Long-term low-dose warfarin therapy is highly effective in preventing stroke in patients with nonrheumatic AF, and can be quite safe with careful monitoring.</p> |
| SPINAF (1995) | <p>Aim: to determine the efficacy of warfarin for the prevention of stroke in neurologically normal patients with nonrheumatic AF.</p> <p>Study: 525 patients were randomly assigned to receive warfarin or placebo. The goal of warfarin therapy was the maintenance of the patient's prothrombin time ratio within the range of 1.2 to 1.5, corresponding to an International Normalized Ratio of approximately 1.4 to 2.8. All patients were followed for 3 years or until termination of the study. The primary end point was clinically evident cerebral infarction. Low-intensity anticoagulation with warfarin prevented cerebral infarction in patients with nonrheumatic atrial fibrillation without producing an excess risk of major hemorrhage. This benefit extended to patients over 70 years of age.</p> |

| | |
|----------------------------|---|
| EAF (1993) | <p>Aim: To assess the preventive benefit of anticoagulation or aspirin in patients with AF and a recent TIA or minor ischaemic stroke</p> <p>Study: 1007 patients with nonrheumatic AF and recent TIA or minor ischaemic stroke were randomised to open anticoagulation or double-blind treatment with either 300 mg aspirin per day or placebo (group 1). Patients with contraindications to anticoagulation were randomised to receive aspirin or placebo (group 2). The measure of outcome was death from vascular disease, any stroke, myocardial infarction, or systemic embolism. Anticoagulation is effective in reducing the risk of recurrent vascular events in nonrheumatic AF patients with recurrent TIA or minor ischemic stroke.</p> |
| SPAF (1991) | <p>Aim: To compare between warfarin and aspirin for ischemic stroke prevention in AF.</p> <p>Study: 1,330 patients with constant or intermittent AF were randomly assigned to aspirin (325 mg/day) or warfarin with placebo for prevention of ischemic stroke and systemic embolism (primary events) during a mean follow-up of 1.3 years. Aspirin and warfarin are both effective in reducing ischemic stroke and systemic embolism in patients with AF. Because warfarin-eligible patients composed a subset of all aspirin-eligible patients, the magnitude of reduction in events by warfarin versus aspirin cannot be compared. Patients with nonrheumatic AF who can safely take either aspirin or warfarin should receive prophylactic antithrombotic therapy to reduce the risk of stroke.</p> |
| SPAF-II (1994) | <p>Aim: To compare between warfarin and aspirin for ischemic stroke prevention in AF.</p> <p>Study: 1100 adults > 60 years of age with AF in the preceding 12 months without prosthetic heart valves, mitral stenosis were randomly assigned to warfarin and aspirin. Warfarin is superior to aspirin in high risk patients to reduce primary endpoint of stroke and systemic embolism. Aspirin alone safe in lower risk patients (age < 75, no hypertension or prior embolism).</p> |
| SPAF-III (1996) | <p>Aim: To evaluate the evidence supporting the use of warfarin and/or aspirin for stroke prevention in patients with AF.</p> |

| | |
|---------------------------------|---|
| | <p>Study: 1044 adults > 60 years of age with AF without prosthetic heart valves, mitral stenosis were randomly assigned to: (1) warfarin adjusted to create an INR between 2.0 and 3.0, or (2) aspirin (325 mg/day); or (3) low-dose warfarin (INR between 1.2 and 1.5) plus aspirin (325 mg/day). Low-intensity, fixed-dose warfarin plus aspirin in this regimen is insufficient for stroke prevention in patients with non-valvular AF at high-risk for thromboembolism; adjusted-dose warfarin (target INR 2.0-3.0) importantly reduces stroke for high-risk patients.</p> |
| ORBIT-AF Registry (2013) | <p>Aim: To identify "real world" treatment patterns of AF.</p> <p>Study: 10,126 patients with AF receiving OAC are often treated with concomitant ASA, even when they do not have cardiovascular disease. Use of OAC + ASA was associated with significantly increased risk for bleeding, emphasizing the need to carefully determine if and when the benefits of concomitant ASA outweigh the risks in AF patients already on OAC.</p> |
| NOACs in AF: | |
| RE-LY (2009) | <p>Aim: To compare two fixed doses of dabigatran with warfarin in patients who had AF and were at increased risk for stroke.</p> <p>Study: 18,113 patients who had AF and a risk of stroke were randomly assigned to receive dabigatran (110 mg or 150 mg twice daily) or adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism. Dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.</p> |
| ARISTOTLE (2011) | <p>Aim: To determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or systemic embolism among patients with AF and at least one other risk factor for stroke.</p> |

| | |
|--------------------------|---|
| | <p>Study: 18,201 patients with AF and at least one additional risk factor for stroke were randomly assigned to apixaban (at a dose of 5 mg twice daily) and warfarin (target INR, 2-3). The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The median duration of follow-up was 1.8 years. Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.</p> |
| AVERROES (2011) | <p>Aim: To evaluate treatment with the apixaban compared with aspirin among patients with AF who were unsuitable for warfarin therapy.</p> <p>Study: 5599 patients with AF who were at increased risk for stroke and for whom VKA therapy was unsuitable were randomly assigned to receive apixaban (5 mg twice daily) or aspirin (81-324 mg/day), to determine whether apixaban was superior. The mean follow-up period was 1.1 years. Apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.</p> |
| ROCKET-AF (2011) | <p>Aim: To evaluate treatment with rivaroxaban compared with warfarin among patients with nonvalvular AF.</p> <p>Study: 14,264 patients with nonvalvular AF who were at increased risk for stroke were randomly assigned to receive either rivaroxaban (20 mg daily) or dose-adjusted warfarin. Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.</p> |
| RIVER (2020) | <p>Aim: To assess the safety and efficacy of rivaroxaban compared with warfarin for patients with a bioprosthetic mitral valve and AF or flutter.</p> <p>Study: 1005 patients with AF and a bioprosthetic mitral valve were randomly assigned to rivaroxaban (20 mg once daily) with dose-adjusted warfarin (target INR, 2.0 to 3.0). The primary outcome was a composite of death, MACE, or major bleeding at 12 months. Rivaroxaban was non inferior to warfarin with respect to the mean time until the primary outcome of death, MACE, or major bleeding at 12 months.</p> |
| ENGAGE AF-TIMI 48 | <p>Aim: To study the safety and efficacy of edoxaban as compared with warfarin in the treatment of AF.</p> |

| | |
|---|---|
| (2013) | Study: 21,105 patients with moderate-to-high-risk AF were randomly assigned to edoxaban or warfarin (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. Edoxaban was noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from CV causes. |
| ELDERCARE-AF (2020) | Aim: To assess the safety and efficacy of low-dose edoxaban among Japanese patients ≥ 80 years of age who had nonvalvular AF and in whom standard oral anticoagulants were not recommended. Study: 984 elderly Japanese patients (≥ 80 years of age) with nonvalvular AF who were not considered to be appropriate candidates for OAC were randomly assigned in a 1:1 ratio to receive a daily dose of 15 mg of edoxaban or placebo. Edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding than placebo. |
| Anticoagulation in special situations: | |
| BRIDGE (2015) | Aim: To compare a strategy of anticoagulation interruption with LMWH bridge therapy among patients with AF undergoing invasive procedure . Study: 1884 patients with AF were randomly assigned to receive bridging anticoagulation therapy with LMWH (Dalteparin 100 IU/kg) or matching placebo administered S.C twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. Follow-up of patients continued for 30 days after the procedure. In patients who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism and decreased the risk of major bleeding. |
| AFIRE (2019) | Aim: To compare rivaroxaban monotherapy with rivaroxaban/antiplatelet therapy among patients with AF and stable coronary artery disease . |

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| | <p>Study: 2236 patients with AF who had undergone PCI or CABG more than 1 year earlier or who had angiographically confirmed coronary artery disease not requiring revascularization were randomly assigned to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent. Rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in patients with atrial fibrillation and stable coronary artery disease.</p> |
| <p>Left Atrial Appendage (LAA) Occlusion/Excision:</p> | |
| <p>PROTECT-AF (2009)</p> | <p>Aim: To determine whether a local strategy of mechanical LAA closure was noninferior to warfarin.</p> <p>Study: 1065 adult patients with non-valvular atrial fibrillation were randomly assigned in a 2:1 ratio to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention) or to warfarin treatment with a target INR between 2.0 and 3.0 (control). The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular AF.</p> |
| <p>PREVAIL (2014)</p> | <p>Aim: To evaluate percutaneous LAA closure compared with long-term warfarin among patients with atrial fibrillation (AF).</p> <p>Study: 407 Patients with nonvalvular AF and CHADS2 score ≥ 2 were randomized to percutaneous LAA closure with the WATCHMAN device and discontinuation of warfarin versus long-term warfarin therapy. Primary endpoints were (i) Death, ischemic stroke, systemic embolism, or (ii) procedure/device-related complication requiring major intervention at 7 days, CV/unexplained death, stroke, or systemic embolism at 18 months, Stroke or systemic embolism from 7 days to 18 months. Among patients with AF, percutaneous closure of the LAA was noninferior to warfarin at preventing stroke or systemic embolism from 7 days to 18 months; however, noninferiority was unable to be established in regard to CV/unexplained death, stroke, or systemic embolism</p> |

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| | <i>at 18 months. Compared with the earlier PROTECT-AF trial, there was improved procedural implant success with reduced device-related complications.</i> |
| PRAGUE-17 (2020) | <p>Aim: <i>To evaluate left atrial appendage occlusion compared with a NOAC among patients with nonvalvular AF.</i></p> <p>Study: <i>402 patients with nonvalvular atrial fibrillation were randomized to left atrial appendage occlusion versus a NOAC. LAA occlusion was noninferior to a NOAC (apixaban) at preventing net ischemic/bleeding events.</i></p> |
| LAAOS III (2021) | <p>Aim: <i>To evaluate surgical LAA occlusion compared with no occlusion among patients with AF undergoing cardiac surgery for another indication.</i></p> <p>Study: <i>2379 participants with AF and a CHA₂DS₂-VASc score ≥ 2 who were scheduled to undergo cardiac surgery for another indication were randomly assigned to undergo or not undergo LAA occlusion during surgery; all the participants were expected to receive usual care, including oral anticoagulation, during follow-up. Among participants with AF who had undergone cardiac surgery, the risk of ischemic stroke or systemic embolism was lower with concomitant LAA occlusion performed during the surgery than without it.</i></p> |
| Rate control: | |
| RACE-II (2010) | <p>Aim: <i>To investigate whether lenient rate control would be noninferior to strict rhythm control in patients with permanent AF.</i></p> <p>Study: <i>614 patients with permanent AF to undergo a lenient rate-control strategy (resting heart rate < 110 bpm) or a strict rate-control strategy (resting heart rate < 80 bpm and heart rate during moderate exercise < 110 bpm). The primary outcome was a composite of CV mortality, HF hospitalization, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. In patients with permanent AF, lenient rate control is as effective as strict rate control and is easier to achieve.</i></p> |
| RATE-AF (2020) | Aim: <i>To evaluate digoxin compared with beta-blocker among patients with permanent AF.</i> |

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| | <p>Study: 160 adults aged 60 years or older with AF and HF symptoms randomized to digoxin vs bisoprolol. There was no statistically significant difference in quality of life at 6 months. These findings support potentially basing decisions about treatment on other end points.</p> |
| APAF-CRT (2021) | <p>Aim: To assess whether strict and regular rate control with AV node ablation and biventricular pacemaker (Ablation + CRT) improves survival.</p> <p>Study: 133 patients with severely symptomatic permanent AF > 6 months, narrow QRS (≤ 110 ms) and at least one HF hospitalization in the previous year were randomly assigned to Ablation + CRT or to pharmacological rate control. We hypothesized that Ablation + CRT is superior in reducing the primary endpoint of all-cause mortality. Ablation + CRT was superior to pharmacological therapy in reducing mortality in patients with permanent AF and narrow QRS who were hospitalized for HF, irrespective of their baseline EF.</p> |
| ALTERNATIVE-AF (2022) | <p>Aim: To compare His-bundle pacing (HBP) with biventricular pacing (BVP) following AV node ablation.</p> <p>Study: 50 patients with persistent AF and reduced LVEF ($\leq 40\%$). All patients underwent AV node ablation and received both HBP and BVP. Patients were randomized to either HBP or BVP for 9 months (phase 1), then were switched to the alternative pacing modality for the next 9 months (phase 2). The primary endpoint was change in LVEF. HBP delivers a modest but significant improvement in LVEF in patients with persistent AF, impaired ventricular function, and narrow QRS duration post-AV node ablation compared with BVP. Larger long-term trials are required to confirm the additional improvements in function with HBP.</p> |
| Rhythm control: | |
| RAFF2 (2020) | <p>Aim: To compare the safety and efficacy of procainamide + electrical cardioversion (DCCV) vs. DCCV alone in patients presenting with acute AF.</p> <p>Study: 1,996 eligible patients with acute AF were randomized in a 1:1 factorial design to: (Protocol 1): Attempted pharmacological cardioversion with intravenous procainamide (15 mg/kg over 30 min) followed by electrical cardioversion (up to three shocks each of ≥ 200 J) if necessary, vs. placebo infusion followed by</p> |

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| | <p>electrical cardioversion. (Protocol 2): Among patients requiring DCCV after 30 min of Protocol 1, an open-label comparison of the anterolateral versus anteroposterior pad positions was performed. A drug + shock approach is similar to a shock first approach among low-risk patients presenting to the ED with acute onset of AF; approximately 50% of patients converted to NSR in the drug + shock approach with intravenous procainamide alone. Both approaches were felt to be relatively safe. Among patients needing cardioversion, placement of pads in anterolateral or anteroposterior position resulted in similar efficacy.</p> |
| <p>PACE 7 ACWAS (2019)</p> | <p>Aim: To evaluate delayed compared with early cardioversion among patients with recent-onset AF.</p> <p>Study: 437 patients with new-onset AF were randomized to delayed cardioversion versus early cardioversion. Patients randomized to delayed cardioversion received rate controlling agents and underwent cardioversion in 48 hours, if needed. TEE was not performed in any patient. Long-term anticoagulation was recommended according to the patient's estimated stroke risk. Delayed cardioversion was noninferior to early cardioversion at maintaining AF at 4 weeks. Spontaneous cardioversion occurred in the majority of patients randomized to a delayed strategy before electrical or pharmacological cardioversion was required. This trial does not apply to patients in whom the duration of AF is unknown.</p> |
| <p>AFFIRM (2002)</p> | <p>Aim: To compare initial strategies of rate control and rhythm control for the treatment of AF in older adults.</p> <p>Study: 4060 patients with AF and a high risk of stroke or death were randomly assigned to cardioversion and treatment with antiarrhythmic drugs and to rate-controlling drugs. Management of AF with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy.</p> |
| <p>EAST-AFNET 4 (2020)</p> | <p>Aim: To compare a rhythm-control strategy vs. usual care (rate control in the majority of cases) among patients with a recent diagnosis of AF.</p> <p>Study: 2789 patients who had early AF (diagnosed ≤ 1 year before enrollment) and CV conditions were randomly assigned to receive either early rhythm control or usual care. Early rhythm control included treatment with antiarrhythmic drugs or AF ablation after randomization. Usual care limited rhythm control to the</p> |

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| | <i>management of AF-related symptoms. Early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early AF and cardiovascular conditions.</i> |
| ATHENA (2009) | <p>Aim: <i>To assess the safety and efficacy of dronedarone in the treatment of AF and atrial flutter (Afl).</i></p> <p>Study: <i>4628 patients were randomly assigned to receive dronedarone, 400 mg twice a day, or placebo. The primary outcome was the first hospitalization due to cv events or death. Dronedarone reduced the incidence of hospitalization due to cv events or death in patients with AF.</i></p> |
| PALLAS (2011) | <p>Aim: <i>To test whether dronedarone would reduce rates of major vascular events or unplanned hospitalization for CV causes in patients with permanent AF who were at high risk for vascular events.</i></p> <p>Study: <i>3236 patients > 65 years with at least a 6-month history of permanent AF and risk factors for major vascular events to receive dronedarone or placebo. The first primary outcome was stroke, MI, systemic embolism, or CV mortality. Dronedarone increased rates of heart failure, stroke, and CV mortality in patients with permanent AF who were at risk for major vascular events.</i></p> |
| Ablation: | |
| APAF (2006) | <p>Aim: <i>To evaluate treatment with pulmonary vein ablation compared with antiarrhythmic drugs among patients with paroxysmal AF.</i></p> <p>Study: <i>198 patients were randomized to circumferential pulmonary vein ablation or to antiarrhythmic medical therapy with flecainide, sotalol or amiodarone. The primary endpoints were Freedom from recurrent atrial arrhythmias. Circumferential pulmonary vein ablation is more successful than ADT for prevention of PAF with few complications.</i></p> |
| ThermoCool- AF (2010) | <p>Aim: <i>To determine the efficacy of catheter ablation compared with antiarrhythmic drug therapy in treating symptomatic paroxysmal AF.</i></p> <p>Study: <i>167 patients with symptomatic AF were randomized in a 2:1 fashion to either catheter ablation, or a previously unused antiarrhythmic drug (Vaughn class I or III). Among patients with paroxysmal AF who had not</i></p> |

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| | <i>responded to at least 1 antiarrhythmic drug, the use of catheter ablation compared with ADT resulted in a longer time to treatment failure during the 9-month follow-up period.</i> |
| MANTRA-PAF (2012) | <p>Aim: <i>To evaluate initial strategy of radiofrequency catheter ablation compared with antiarrhythmic drug among patients with paroxysmal AF.</i></p> <p>Study: <i>294 patients with paroxysmal AF and no history of antiarrhythmic drug use were randomly assigned to an initial treatment strategy of either radiofrequency catheter ablation or therapy with class IC or class III antiarrhythmic agents. Follow-up included 7-day Holter-monitor recording at 3, 6, 12, 18, and 24 months. No significant difference was found in the AF burden over a period of 2 years.</i></p> |
| CABANA (2021) | <p>Aim: <i>To compare the safety and efficacy of catheter ablation compared with drug therapy for the treatment of new-onset or untreated AF</i></p> <p>Study: <i>2204 patients with AF who were ≥ 65 years old or < 65 years old with ≥ 1 risk factor for stroke were randomly assigned to ablation with pulmonary vein isolation or drug therapy including rate or rhythm control drugs. The primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. Catheter ablation produced clinically important improvements in survival, freedom from AF recurrence, and quality of life relative to drug therapy.</i></p> |
| EARLY-AF (2021) | <p>Aim: <i>To evaluate catheter cryoballoon ablation compared with antiarrhythmic drug therapy among patients with paroxysmal AF.</i></p> <p>Study: <i>303 patients with symptomatic, paroxysmal, untreated AF were randomly assigned to undergo catheter ablation with a cryothermy balloon or to receive antiarrhythmic drug therapy for initial rhythm control. All the patients received an implantable cardiac monitoring device to detect atrial tachyarrhythmia. The follow-up period was 12 months. There was a significantly lower rate of AF recurrence with catheter cryoballoon ablation than with antiarrhythmic drug therapy, as assessed by continuous cardiac rhythm monitoring.</i></p> |
| FIRE AND ICE (2016) | Aim: <i>To evaluate pulmonary vein isolation with cryoballoon ablation versus radiofrequency ablation among patients with paroxysmal AF.</i> |

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| | <p>Study: 762 patients with drug-refractory paroxysmal AF were randomized to cryoballoon ablation and to radiofrequency ablation. The mean duration of follow-up was 1.5 years. Cryoballoon ablation was noninferior to radiofrequency ablation with respect to efficacy, and there was no significant difference between the two methods with regard to overall safety.</p> |
| AATAC (2016) | <p>Aim: To evaluate catheter ablation compared with amiodarone among patients with persistent AF and heart failure.</p> <p>Study: Patients with persistent AF, dual-chamber ICD or CRT-D, NYHA II to III, and LVEF < 40% within the past 6 months were randomly assigned to undergo catheter ablation for AF or receive amiodarone. Recurrence of AF was the primary end point. All-cause mortality and unplanned hospitalization were the secondary end points. Patients were followed up for a minimum of 24 months. Catheter ablation of AF is superior to amiodarone in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with heart failure and persistent AF.</p> |
| CASTLE-AF (2018) | <p>Aim: To evaluate catheter ablation compared with standard treatment among patients with LV dysfunction and AF.</p> <p>Study: 363 patients with symptomatic paroxysmal or persistent AF who did not have a response to antiarrhythmic drugs, had unacceptable side effects, or were unwilling to take these drugs were randomly assigned to undergo either catheter ablation or medical therapy (rate or rhythm control) for AF in addition to guidelines-based therapy for heart failure. All the patients had NYHA class II, III, or IV heart failure, a LVEF ≤ 35%, and an implanted defibrillator. Catheter ablation for AF in patients with HF was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening HF than was medical therapy.</p> |
| CASTLE HTx (2023) | <p>Aim: To assess the role of catheter ablation in patients with symptomatic AF and end-stage heart failure.</p> <p>Study: 194 patients with symptomatic AF and end-stage heart failure who were referred for heart transplantation evaluation were assigned to receive catheter ablation and guideline-directed medical therapy</p> |

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| | <p>or medical therapy alone. The primary end point was a composite of death from any cause, implantation of a LVAD or urgent heart transplantation. The trial was stopped for efficacy by the data and safety monitoring board 1 year after randomization was completed. The combination of catheter ablation and guideline-directed medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a LVAD, or urgent heart transplantation than medical therapy alone.</p> |
| <p>AMICA (2019)</p> | <p>Aim: To demonstrate the superiority of the catheter ablation strategy in terms of the absolute increase in LVEF from baseline to 1 year.</p> <p>Study: 140 Patients with persistent/longstanding persistent AF and LVEF $\leq 35\%$ were randomly allocated to catheter ablation of AF or best medical therapy (BMT). The primary study end point was the absolute increase in LVEF from baseline at 1 year. The AMICA trial did not reveal any benefit of catheter ablation in patients with AF and advanced HF. This was mainly because of the fact that at 1 year, LVEF increased in ablation patients to a similar extent as in BMT patients. The effect of catheter ablation of AF in patients with HF may be affected by the extent of HF at baseline, with a rather limited ablation benefit in patients with seriously advanced HF.</p> |
| <p>Subclinical AF:</p> | |
| <p>ASSERT (2012)</p> | <p>Aim: To evaluate whether subclinical episodes of rapid atrial rate detected by implanted devices were associated with an increased risk of ischemic stroke in patients who did not have other evidence of AF.</p> <p>Study: 2580 patients ≥ 65 year of age, with hypertension and no history of AF, in whom a pacemaker or defibrillator had recently been implanted, were monitored for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 bpm for > 6 min) and followed for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischemic stroke or systemic embolism.</p> |

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| NOAH-AFNET 6 (2023) | <p>Aim: <i>To demonstrate whether the occurrence of AHREs in patients without AF justifies the initiation of anticoagulants.</i></p> <p>Study: <i>2536 patient ≥ 65 years of age who had AHREs lasting for at least 6 minutes and who had at least one additional risk factor for stroke were randomly assigned to receive edoxaban or placebo. The primary efficacy outcome was a composite of CV death, stroke, or systemic embolism, evaluated in a time-to-event analysis. The safety outcome was a composite of death from any cause or major bleeding. Among patients with AHREs detected by implantable devices, anticoagulation with edoxaban did not significantly reduce the incidence of a composite of CV death, stroke, or systemic embolism as compared with placebo, but it led to a higher incidence of a composite of death or major bleeding. The incidence of stroke was low in both groups.</i></p> |
| ARTESIA (2023) | <p>Aim: <i>To determine whether apixaban would result in a lower risk of stroke or systemic embolism than aspirin in patients with subclinical AF.</i></p> <p>Study: <i>4012 patients with subclinical atrial fibrillation lasting 6 minutes to 24 hours. Patients were randomly assigned in a double-blind, double-dummy design to receive apixaban at a dose of 5 mg twice daily (2.5 mg twice daily when indicated) or aspirin at a dose of 81 mg daily. The primary efficacy outcome, stroke or systemic embolism, was assessed in the intention-to-treat population; the primary safety outcome, major bleeding, was assessed in the on-treatment population. apixaban resulted in a lower risk of stroke or systemic embolism than aspirin but a higher risk of major bleeding.</i></p> |

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Chapter 17:

Ventricular Arrhythmia

Definitions and Classification:

- **Ventricular arrhythmia subtypes:**

- **Premature ventricular complex (PVC):** Premature occurrence of an abnormal QRS complex (duration typically ≥ 120 ms, corresponding T-wave typically broad and in the opposite direction of the major QRS deflection, no preceding P-wave).
- **Unifocal or monomorphic PVCs:** PVCs with a single QRS morphology.
- **Multifocal, multiform, or polymorphic PVCs:** PVCs with different QRS morphologies.
- **Short-coupled PVC:** A PVC that interrupts the T-wave of the preceding conducted beat.
- **Bigeminy** means the alternation of one sinus beat with one PVC; **trigeminy** means the occurrence of one PVC after every two sinus beats. This is different from **couplet** (two PVCs in a row), or **triplet** (three PVCs in a row).
- **Ventricular tachycardia (VT):** ≥ 3 consecutive beats with a rate > 100 b.p.m.⁽¹⁾ originating from the ventricles, independent from atrial and AV nodal conduction.

VT can be classified according to duration:

- **Non-sustained VT (NSVT):** Run of consecutive ventricular beats persisting for 3 beats to 30 s.
- **Sustained VT:** Continuous VT for at least 30 s, or which requires an intervention for termination.
- **Electrical storm:** ≥ 3 episodes of sustained VT within 24 hours (separated by at least 5 min), each requiring termination by either anti-tachycardia pacing (ATP) or cardioversion/defibrillation.
- **Incessant VT:** Continuous sustained VT that recurs promptly despite repeated intervention for termination over several hours.

(1) A ventricular rhythm slower than 100 bpm is accelerated idioventricular rhythm (AIVR); a ventricular rhythm slower than 40 bpm is a ventricular escape rhythm. AIVR may be seen in: (1) acute ischemia (whether reperfused or not), (2) up to 8% of HF cases and cardiomyopathies, (3) digoxin or antiarrhythmic drug toxicity, and (4) electrolyte abnormalities (hyperkalemia). There is no convincing evidence linking AIVR to VT/VF, and thus no specific treatment for AIVR is necessary.

VT can be classified according to morphology:

- **Monomorphic VT (MVT):** Same QRS morphology from beat to beat.
- **Polymorphic VT (PVT):** is a VT that has two or more QRS morphologies.
- **Bidirectional VT:** Beat to beat alternation of the frontal QRS axis (e.g., in catecholaminergic polymorphic ventricular tachycardia [CPVT], Andersen-Tawil, digoxin toxicity, acute myocarditis).
- **Torsades de pointes VT (TdP):** Subtype of polymorphic VT in the context of QT prolongation with continually changing QRS complexes that appear to spiral around the baseline of the ECG lead in a sinusoidal pattern.
- **Ventricular fibrillation (VF):** A chaotic rhythm with undulations that are irregular in timing and morphology, without discrete QRS complexes on the surface ECG.
- **Sudden Cardiac death:**
 - **Sudden cardiac arrest (SCA):** Sudden cessation of normal cardiac activity with haemodynamic collapse.
 - **Sudden cardiac death (SCD):** Sudden natural death presumed to be of cardiac cause that occurs within 1 h of onset of symptoms in witnessed cases, and within 24 h of last being seen alive if unwitnessed.
SCD in autopsied cases is defined as the natural unexpected death of unknown or cardiac cause.
 - **Sudden infant death syndrome (SIDS):** Unexplained sudden death occurring in an individual younger than 1 year with negative pathological, toxicological and forensic assessment.
 - **Sudden arrhythmic death syndrome (SADS):** Unexplained sudden death occurring in an individual older than 1 year with negative pathological and toxicological assessment. Note: Synonymous with 'autopsy-negative sudden unexplained death'.
- **Syncope:**
 - **Unexplained syncope:** Transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery, but unexplained after workup.
 - **Arrhythmic syncope:** as above, but highly suspicious for intermittent bradycardia, rapid supraventricular tachycardia (SVT), or VA.

- **Genetics:** The American College of Medical Genetics has provided a framework for the interpretation of disease causation by genetic variants standardized into five classes: **V** 'pathogenic'; **IV** 'likely pathogenic'; **III** 'variant of uncertain significance'; **II** 'likely benign'; and **I** 'benign'.
- **Pathogenic variant:** genetic variants most likely to cause an associated disease.
- **Variant of uncertain significance:** A change in a gene's DNA sequence that has an unknown effect on a person's health.
- **Site of origin of the PVC:** (*PVC looks away, i.e., looks negative, from where it originates*)
- **Right vs. left:**
 - RV origin → LBBB morphology
 - LV origin → RBBB morphology
- **Anterior vs. inferior:**
 - Anterior origin → QRS (+) in the inferior leads (vertical axis).
 - Inferior origin → QRS (–) in the inferior leads (left axis).
- **Basal vs. apical:**
 - Basal origin → QRS is upright in all precordial leads, and (–) in I-aVL if lateral origin.
 - Apical origin → QRS is negative in all precordial leads, as it looks away from them, esp. V₃-V₆.

Diagnostic tools:

- **History and physical examination:**
 - History should focus on 'red flags', including features of arrhythmic syncope, e.g., absence of vagal prodrome, and family history of premature or SCD.
 - Specific skin features may be relevant, e.g., Lupus pernio, erythema nodosum in sarcoidosis, angiokeratoma in Fabry's disease, xanthelasma/xanthoma, and palmoplantar keratosis in ARVC.
- **Laboratory testing:** Natriuretic peptides may have a role in the identification of individuals at increased risk of SCD in the general population or in patients with CAD.
- **Non-invasive and invasive tests:**

- **ECG and ambulatory ECG monitoring:** The 12-lead ECG is an important tool for the diagnosis of underlying disease, diagnosis of the VA subtype, and for risk stratification in selected populations. Holter monitoring over a period of 24–48 h is appropriate for daily arrhythmias, while intermittent monitoring over a longer period, with patient-activated ECG recorders (or mobile-health/smartphones), should be preferred for infrequent events. Implantable loop recorders (ILR) can be useful in diagnosing arrhythmias in patients with unexplained syncope.
- **Signal-averaged ECG (SaECG)** is a special ECG technique, in which multiple electric signals from the heart are averaged to remove interference and reveal small variations in the QRS complex. It is done using an ECG machine equipped with SAECG software. SAECG recording requires a few minutes (usually about 7-10 min), as the machine must record multiple subsequent QRS potentials to remove interference due to skeletal muscle and to obtain a statistically significant average trace. Finally, SAECG recording yields a single, averaged QRS potential, usually printed in a much larger scale than standard ECGs, upon which the SAECG software performs calculations to reveal very low amplitude signals ($< 40 \mu\text{V}$) in the final portion of the QRS complex (the so-called "late ventricular potentials"). These can be immediately interpreted by comparing results with cut-off values. SaECG can contribute to the diagnosis of ARVC.
- **Exercise testing** is useful for the diagnosis and for evaluating response to therapy in patients with suspected/proven adrenergic-dependent rhythm disturbances (e.g exercise-induced VT in CPVT).
The 4-minute recovery QTc after exercise testing can contribute to the diagnosis LQTS.
- **Imaging** is crucial to assess cardiac function and detect cardiomyopathies. A negative imaging study supports primary electrical disease in a patient with VA.
- **Provocative diagnostic tests:** Common tests performed are:
 - Sodium channel blocker testing for Brugada syndrome (BrS).
 - Adenosine test to exclude latent pre-excitation.
 - Epinephrine challenge may be useful in CPVT when exercise cannot be performed. Epinephrine test is not recommended for LQTS due to the high false positive rate and utility of exercise testing.

- intracoronary doses of acetylcholine/ergonovine for diagnosis of coronary vasospasm as a cause of VF in the absence of obstructive coronary diseases/cardiomyopathy.
- **EP studies** including programmed electrical stimulation (PES), and electroanatomical mapping:
 - PES is mainly employed to confirm the diagnosis of VT and induce mappable VAs with non-inducibility being an ablation endpoint. In patients with SHD and mildly reduced or preserved LVEF who present with unexplained syncope, induction of SMVT with PES ⁽¹⁾ can be helpful to identify the underlying cause and to predict subsequent events.
 - Endocardial mapping may be helpful in the differentiation of ARVC from benign outflow tract VT and for targeting biopsy in suspected myocarditis, ARVC, and sarcoidosis cases.
- **Genetic testing:**

A mutation (Class IV or V variant) can be used immediately either for confirmation of diagnosis in probands (the first affected family member), or for initial diagnosis of relatives. A negative result does not exclude a diagnosis and should not be used for this purpose.

| Table 17-1: ESC Recommendations for genetic testing for evaluation of VA: | | |
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| Recommendations | Class | Level |
| <i>Genetic testing is recommended when a condition is diagnosed in a living or deceased individual with a likely genetic basis and a risk of VA and SCD.</i> | I | B |
| <i>When a putative causative variant is first identified, evaluation for pathogenicity is recommended using an internationally accepted framework.</i> | I | C |
| <i>When a Class IV or Class V variant has been identified in a living or deceased individual with a condition that carries a risk of VA and SCD, genetic testing of first-degree and symptomatic relatives and obligate carriers is recommended.</i> | I | C |

(1) PVT/VF induction in SHD is in general considered as a non-specific finding.

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| <i>It is recommended that Class III and Class IV variants should be evaluated for segregation in families where possible, and the variant re-evaluated periodically.</i> | I | C |
| <i>It is not recommended to undertake genetic testing in index patients with insufficient evidence of a genetic disease.</i> | III | C |

Table 17-2: Intravenous provocative diagnostic tests:

| Diagnostic test | Indications | Dose | Positive test | Contraindications | When to stop | Observation time |
|---|--|--|---|--|--|---|
| Ajmaline Or Flecainide | -Family history of BrS or SADS -Resuscitated CA without SHD | - Ajmaline: 1 mg/kg over 10 min (max. 100 mg) - Flecainide: 2 mg/kg over 10 min (max. 150 mg) | BrS type 1 ECG | - Type 1 BrS - HF - Precaution if evidence of conduction disease | - VT/VF (if developed, give IV isoprenaline, Na bicarbonate) - Type 1 BrS - PVCs - QRS widening > 150% | - 30 min if negative - 4 hrs if positive |
| Epinephrine | -CPVT and resuscitated CA when exercise test not feasible -Family history of SADS | Start at 0.025 µg/kg/min for 10 min Increase sequentially to 0.05, 0.1 and 0.2 µg/kg/min. | ≥ 3 beats of PVT <u>or</u> bidirectional VT | QTc prolongation ≥ 480 ms | - SBP ≥ 200, - NSVT, or PVT - > 10 PVCs/min., - T wave alternans, or - Patient intolerance. If symptoms persist after discontinuation, I.V metoprolol | 30 min. |

| | | | | | | |
|--|--|--|--|--|---|--|
| | | | | | 2.5-5mg over 1 min. | |
| Adenosine | <i>Exclude latent pre-excitation</i> | <i>6, 12, 18 mg boluses (up to max. 24 mg)</i> | <i>Identification of accessory pathway</i> | <i>Asthma, sinus node disease, allergy to adenosine</i> | <ul style="list-style-type: none"> - Bronchospasm, bradycardia, asystole, AF, seizures - Antagonist: Theophylline | <i>5 min.</i> |
| Acetylcholine Or Ergonovine | <i>Suspicion of coronary vasospasm</i> | <i>Intracoronary RCA: Up to 50 µg LCA: Up to 100 µg over 20 s.</i> | <i>Coronary spasm</i> | <ul style="list-style-type: none"> - LM stenosis > 50%, 3-vessel, 2-vessel with total occlusion - HF (NYHA III/IV) - Bronchospasm - Renal failure | <i>Temporary pacemaker wire for backup pacing</i> | <i>Normal post procedural observation time</i> |

Diagnostic evaluation at first presentation with VA:

VA and (aborted) SCD are common first manifestations of a previously not known cardiac condition. A comprehensive diagnostic evaluation is provided for five frequently encountered clinical scenarios:

1. Incidental finding of a non-sustained VT (NSVT)
2. First sustained monomorphic VT (SMVT) episode.
3. Sudden cardiac arrest survivors
4. Sudden death victims
5. Relatives of sudden arrhythmic death syndrome decedents.

▪ **Scenario 1: Incidental finding of NSVT:**

- Approximately 1% of asymptomatic individuals without apparent heart disease develop NSVT during exercise testing; in the absence of ST changes on the sinus beats, NSVT does not affect long-term prognosis and is typically a form of monomorphic idiopathic VT.
- In contrast, NSVT is likely an independent predictor of mortality in patients with cardiomyopathy.
- Typical MVT morphologies can suggest an idiopathic origin with favourable prognosis. In contrast, monomorphic NSVT with short cycle length (usually < 300 ms) or short-coupled PVC initiating non-sustained PVT may identify patients at higher risk of SCD.

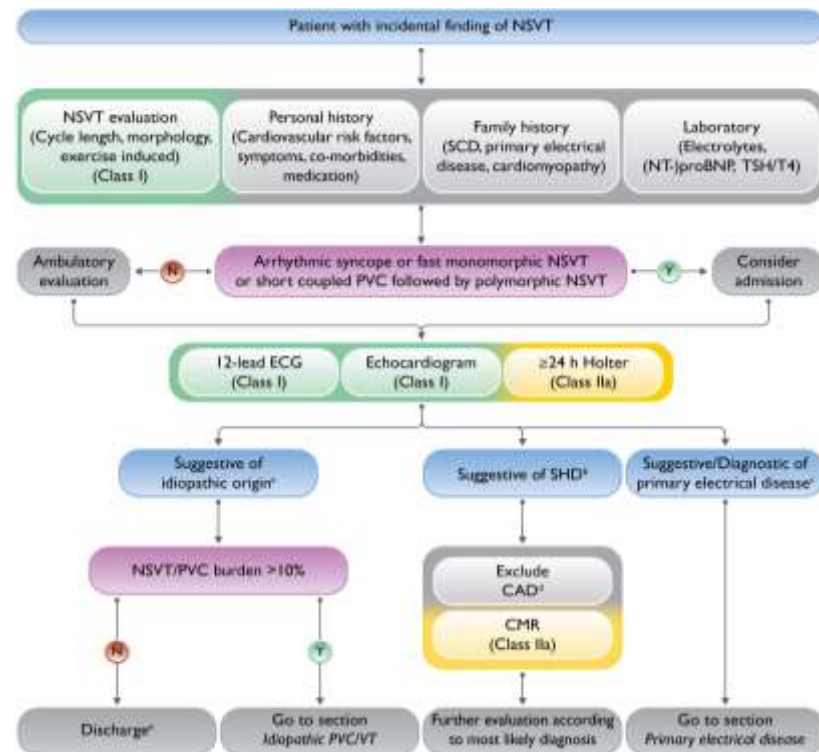


Figure 17-1: Algorithm for the evaluation of patients presenting with an incidental finding of NSVT (a) ECG morphology suggestive of RVOT or fascicular origin, negative family history, normal 12-lead ECG, and echocardiogram. (b) e.g. atrioventricular conduction abnormalities, Q waves, broad QRS complex, ST/T waves deviations, abnormally high or low voltages. Ventricular dysfunction/dilatation/ hypertrophy/wall thinning, wall motion abnormalities, multitopic PVCs/NSVTs/increasing ventricular arrhythmia burden with exercise. (c) e.g. Brugada pattern, long/short QT, polymorphic/bidirectional VA with exercise. (d) Diagnostic test to exclude CAD according to patient profile and symptoms. (e) Consider re-evaluation in case of new symptoms or changes in patient clinical condition. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

- **Scenario 2: First presentation of SMVT:** The majority of patients with SMVT have underlying SHD. SMVT in SHD is mainly due to scar-related re-entry or due to re-entry involving a diseased conduction system or due to focal sources.

N.B: A monomorphic VT occurring in the context of electrolyte abnormalities or antiarrhythmic drugs, or acute ischemia should be evaluated and treated similarly to VT occurring without these factors. These factors, per se, can cause polymorphic rather than monomorphic VT. Keep a low threshold for placing an ICD for monomorphic VT, even in the context of seemingly reversible causes.

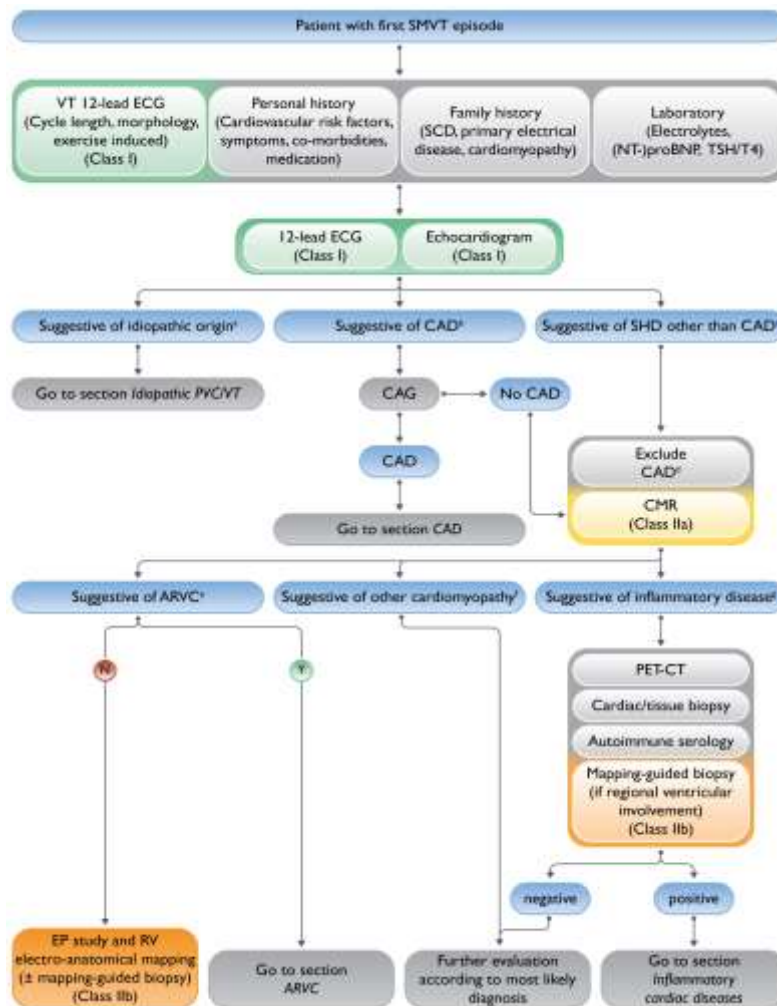


Figure 17-2: Algorithm for the evaluation of patients presenting with an incidental finding of non-sustained ventricular tachycardia. (A) ECG morphology suggestive of RV outflow tract or fascicular origin, negative family history, normal 12-lead ECG, and echocardiogram. (B) e.g., Q waves, QRS fragmentation, ST/T abnormalities, wall motion abnormalities in coronary territories. (C) e.g., atrioventricular (AV) conduction abnormalities, Q waves, broad QRS complex, T-wave inversion, abnormally high or low voltages. Ventricular dysfunction/dilatation/ hypertrophy/wall thinning/wall motion abnormalities/diffuse hypokinesia. (D) Diagnostic test to exclude CAD according to patient profile and symptoms. (E) According to revised task force criteria. (F) e.g., AV conduction abnormalities, abnormally high or low voltages, broad QRS, ST/T wave deviations, LV dilatation and dysfunction, LGE with non-ischaemic distribution. (G) e.g., AV conduction abnormalities, broad QRS, ST/T deviations multifocal PVCs, inflammatory hyperaemia and oedema, fibrosis, LV and RV systolic dysfunction, pericardial effusion. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

▪ **Scenario 3: Sudden cardiac arrest (SCA) survivor:**

There are four potential causes of SCA: **(1)** Non cardiac (e.g brain hemorrhage and pulmonary embolism), **(2)** ischemic heart disease, **(3)** Non ischemic structural heart disease, **(4)** Primary electric diseases.

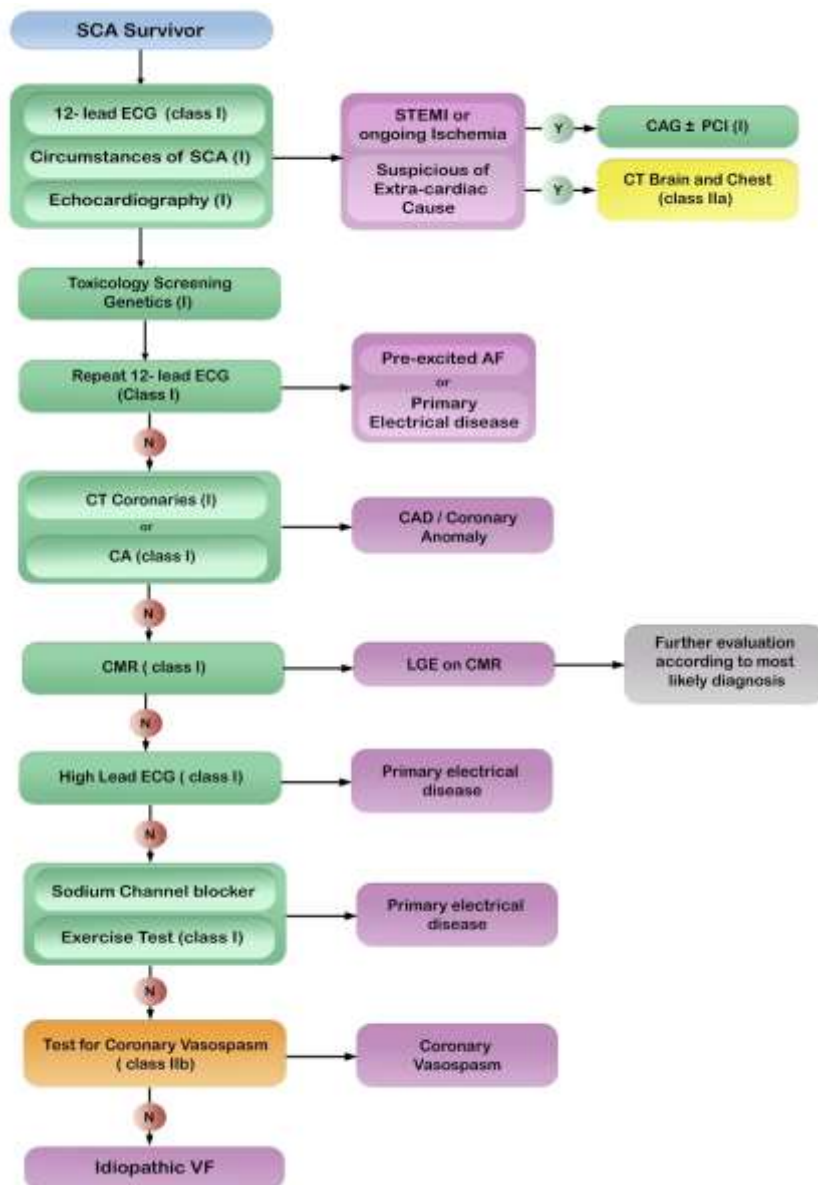


Figure 17-3: Algorithm for the evaluation of sudden cardiac arrest survivors. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

▪ **Scenario 4: Sudden death victim:**

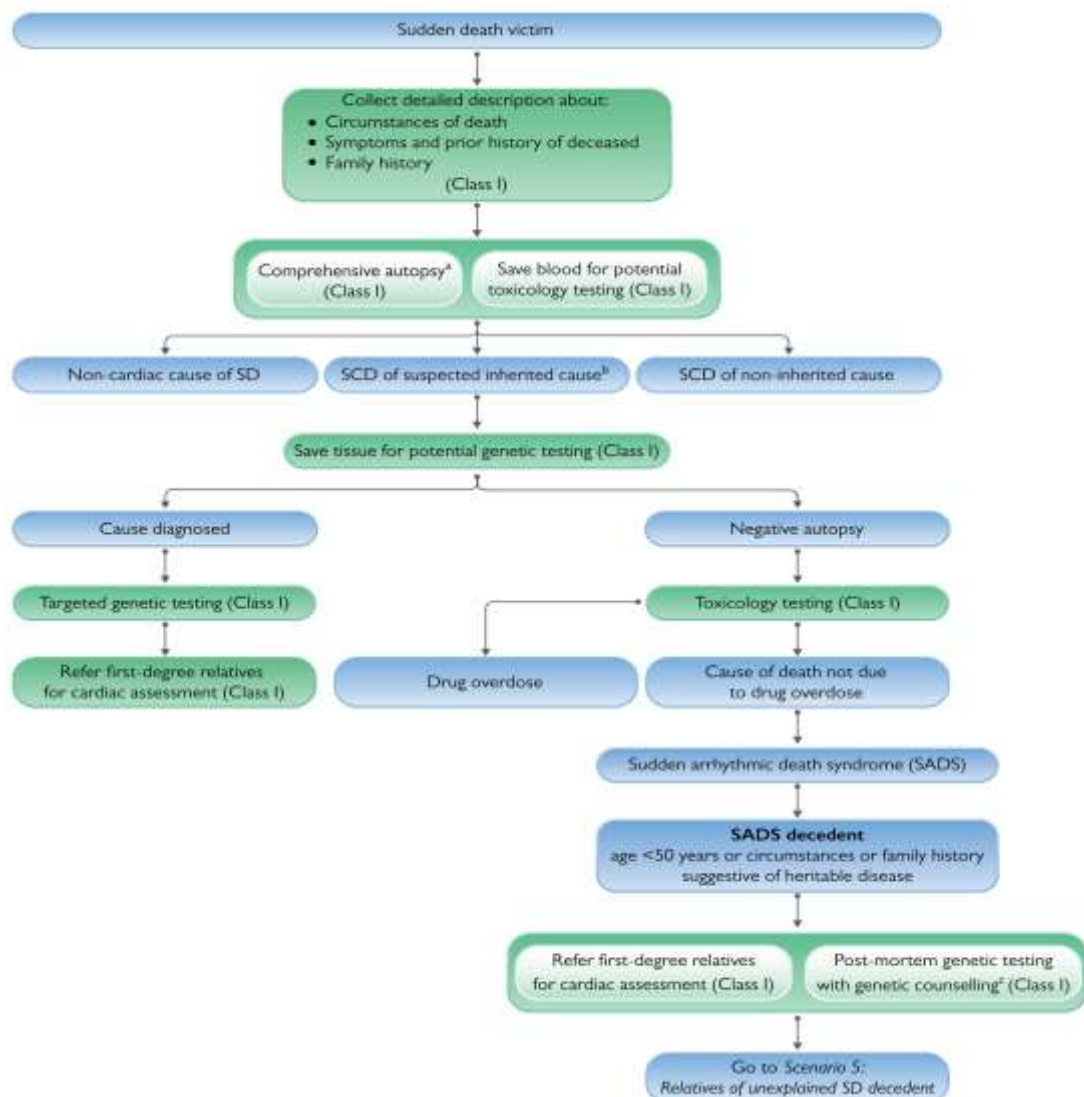


Figure 17-4: Algorithm for the evaluation of sudden death victims. (A) Autopsy is recommended, ideally in all cases of unexpected SD and always in those under 50 years. Autopsy should include full macroscopic examination and histopathology of all organs. The heart should ideally be examined by an expert cardiac pathologist. An expert cardiac pathologist alters the initial diagnosis in 41% of cases. Samples suitable for DNA extraction should be retained when inherited causes or unexplained death are suspected. (B) Based on all circumstances, this includes negative autopsies, autopsies with uncertain findings, non-ischaemic cardiomyopathies, coronary artery disease where familial hypercholesterolaemia is suspected and thoracic aortic dissections. (C) After informed consent of relatives. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

▪ **Scenario 5: Relatives of sudden arrhythmic death syndrome decedents:**

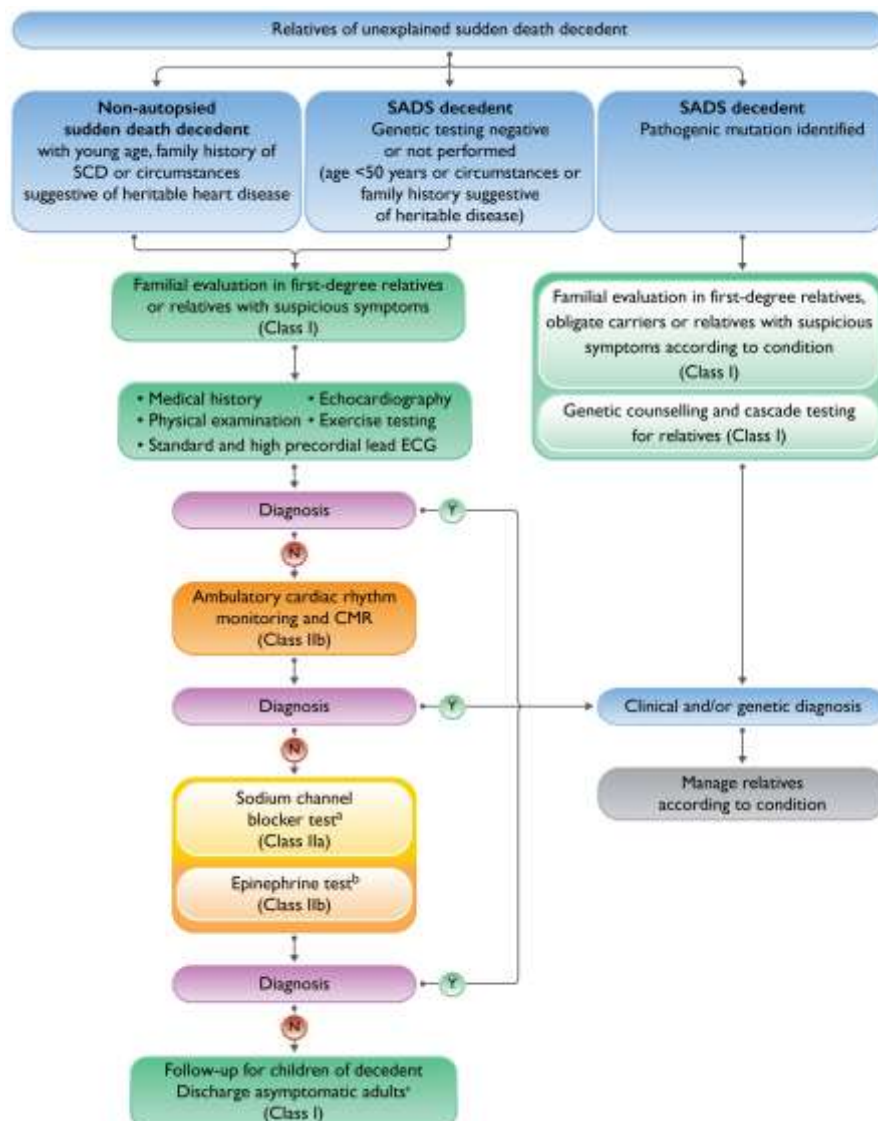


Figure 17-5: Algorithm for the evaluation of relatives of unexplained sudden death decedents. (A) Over 16 years old + any suspicions for Brugada syndrome on tests or decedent circumstances of death. **(B)** If exercise is not feasible. **(C)** Re-evaluate if change in family history or new symptoms. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

| Table 17-3: ESC Recommendations for diagnostic evaluation at first presentation with VA: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Newly documented ventricular arrhythmia: | | |
| In patients with newly documented VA (frequent PVCs, NSVT, SMVT): | | |
| ○ Baseline 12-lead ECG, recording of the VA on 12-lead ECG, whenever possible, and an echocardiogram are recommended as first-line evaluation. | I | C |
| ○ If there is suspicion of SHD other than CAD after evaluation, CMR should be considered. | IIa | B |
| In patients with an incidental finding of a NSVT, a ≥ 24 h Holter ECG should be considered. | IIa | C |
| In patients presenting with a first SMVT episode, EP study, electroanatomical mapping, and mapping-guided biopsies may be considered for aetiological evaluation. | IIb | C |
| Sudden cardiac arrest survivors: | | |
| The investigation of a SCA survivor without obvious extra-cardiac cause is recommended to be overseen by a multidisciplinary team. | I | B |
| In electrically unstable patients after SCA, with suspicion of ongoing myocardial ischaemia, a coronary angiogram is indicated. | I | C |
| In SCA survivors, brain/chest CT scan should be considered when patient characteristics, ECG, and echocardiography are not consistent with a cardiac cause. | IIa | C |
| In SCA survivors, All the following are recommended: | | |
| - collection of blood samples at presentation for potential toxicology and genetic testing | I | B |
| - Retrieval of recordings from CIEDs and wearable monitors | I | B |
| | I | B |

| | | |
|--|--------|--------|
| <ul style="list-style-type: none"> - repeated 12-lead ECGs during stable rhythm (including high precordial lead ECG), as well as continuous cardiac monitoring. - Echocardiography for evaluation of cardiac structure and function | I | C |
| <p><i>in all SCA survivors without a clear underlying cause, it is recommended to:</i></p> <ul style="list-style-type: none"> - Coronary imaging and CMR with LGE for evaluation of cardiac structure and function. - Sodium channel blocker test and exercise testing | I I | B B |
| <i>In SCA survivors, ergonovine, acetylcholine, or hyperventilation testing may be considered for the diagnosis of coronary vasospasm.</i> | IIb | B |
| Sudden death victims: | | |
| <i>Investigation of unexpected SD, especially in case of suspicion of inherited disease, should be made a public health priority.</i> | I | B |
| <i>In cases of SD, it is recommended to collect a detailed description of circumstances of death, symptoms prior to death, the family history, and to review prior medical files.</i> | I | B |
| <i>A comprehensive autopsy is recommended, ideally, in all cases of unexpected SD, and always in those < 50 years of age.</i> | I | B |
| <i>In cases of SCD, it is recommended to retain samples suitable for DNA extraction and consult a cardiac pathologist when an inherited cause is suspected or the cause of death unexplained.</i> | I | B |
| <i>Toxicology screens are recommended in SD cases with uncertain cause of death.</i> | I | B |
| <i>For SCD where the cause is known or suspected to be heritable, genetic testing targeted to the cause is recommended.</i> | I | B |
| <i>Following SADS, post-mortem genetic testing targeted to primary electrical disease is recommended when the decedent is young (< 50) and/or the circumstances and/or family history support a primary electrical disease.</i> | I | B |

| | | |
|--|------------|----------|
| <i>When an autopsy diagnoses possible heritable cardiac disease, it is recommended to refer first-degree relatives for cardiac assessment in a specialized clinic.</i> | I | B |
| <i>In non-autopsied cases of SD where inherited cardiac disease is suspected, it is recommended to refer first-degree relatives for cardiac assessment in a specialized clinic.</i> | I | B |
| <i>Following SADS, post-mortem genetic testing in the decedent for additional genes may be considered.</i> | IIb | C |
| <i>Following SADS, hypothesis-free post-mortem genetic testing using exome or genome sequencing is not recommended.</i> | III | B |
| Relatives of sudden arrhythmic death syndrome decedents: | | |
| <i>Familial evaluation of SADS decedents is recommended:</i> <ul style="list-style-type: none"> ○ <i>For first-degree relatives</i> ○ <i>For relatives who must carry a mutation based on analysis of the family history</i> ○ <i>For relatives with suspicious symptoms</i> ○ <i>When the decedent's age is < 50 years, or if there is other circumstantial data or family history to suggest heritable disease.</i> | I | B |
| <i>Familial evaluation of SADS decedents is recommended to include genetic testing when postmortem genetic testing in a SADS decedent detects a pathogenic mutation.</i> | I | B |
| <i>Baseline familial evaluation of SADS decedents is recommended to include taking a medical history and performing physical examination, standard and high precordial lead ECG, echocardiography, and exercise testing.</i> | I | B |
| <i>In SADS families without a diagnosis after clinical evaluation, follow-up is recommended for children of decedents until they reach adulthood.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Pharmacological testing with a sodium channel blocker should be considered in relatives of SADS decedents who are 16 years or older when baseline testing and/or proband findings increase the suspicion of BrS.</i> | IIa | B |
| <i>Ambulatory cardiac rhythm monitoring and CMR may be considered in relatives of SADS decedents.</i> | IIb | C |
| <i>Pharmacological testing including epinephrine challenge (if exercise testing is impractical) and sodium channel blocker challenge may be considered in first-degree relatives of SADS decedents with normal baseline testing.</i> | IIb | B |
| <i>In SADS families without a diagnosis after clinical evaluation, follow-up is not recommended for asymptomatic adults who can be discharged with advice to return if they develop symptoms or if the family history changes.</i> | III | C |

Acute management of ventricular arrhythmias:

- **Treatment of reversible causes:** Reversible causes may account for up to 50% of SCA. Patients who survive SCA in the context of a presumed reversible cause may have a high mortality rate.
- **Drug-induced arrhythmias** should be suspected in patients being treated with agents known to alter the electrical properties of the heart (e.g. inducing QRS and/or QT prolongation) or causing electrolyte abnormalities (e.g. thiazide and loop diuretics).
- **Electrolyte imbalances:** Hypomagnesaemia and/or hypokalemia may be associated with Torsades de pointes (TdP). IV magnesium is an effective therapy for TdP even in the absence of hypomagnesemia.

Table 17-4: ESC Recommendations for treatment of reversible conditions:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Withdrawal of offending agents is recommended whenever drug-induced VAs is suspected.</i> | I | B |

| | | |
|---|------------|----------|
| <i>Investigation for reversible causes (e.g. electrolyte imbalances, ischemia, hypoxemia, fever) is recommended in patients with VA.</i> | I | C |
| <i>Despite a possible correctable cause for the presenting VA, the need for ICD implantation should be considered based on an individual evaluation of the risk of subsequent VA/SCD.</i> | IIa | C |

▪ **Acute management of sustained monomorphic VT:**

- Documentation of any hemodynamically tolerated wide QRS tachycardia on 12-lead ECG is important.
- Prompt termination of SMVT is recommended even for tolerated SMVT, as rapid hemodynamical deterioration may occur ⁽¹⁾. Termination can be achieved with electrical cardioversion, antiarrhythmic medications, or pacing techniques.
- Administration of adenosine or vagal maneuvers with continuous recording of 12-lead ECG should be considered if SVT is likely. Adenosine may also terminate specific VT subtypes. Such a response indicates triggered activity as the mechanism underlying the arrhythmia.

(1) Cardioversion is not indicated in patients with repetitive NSVTs.

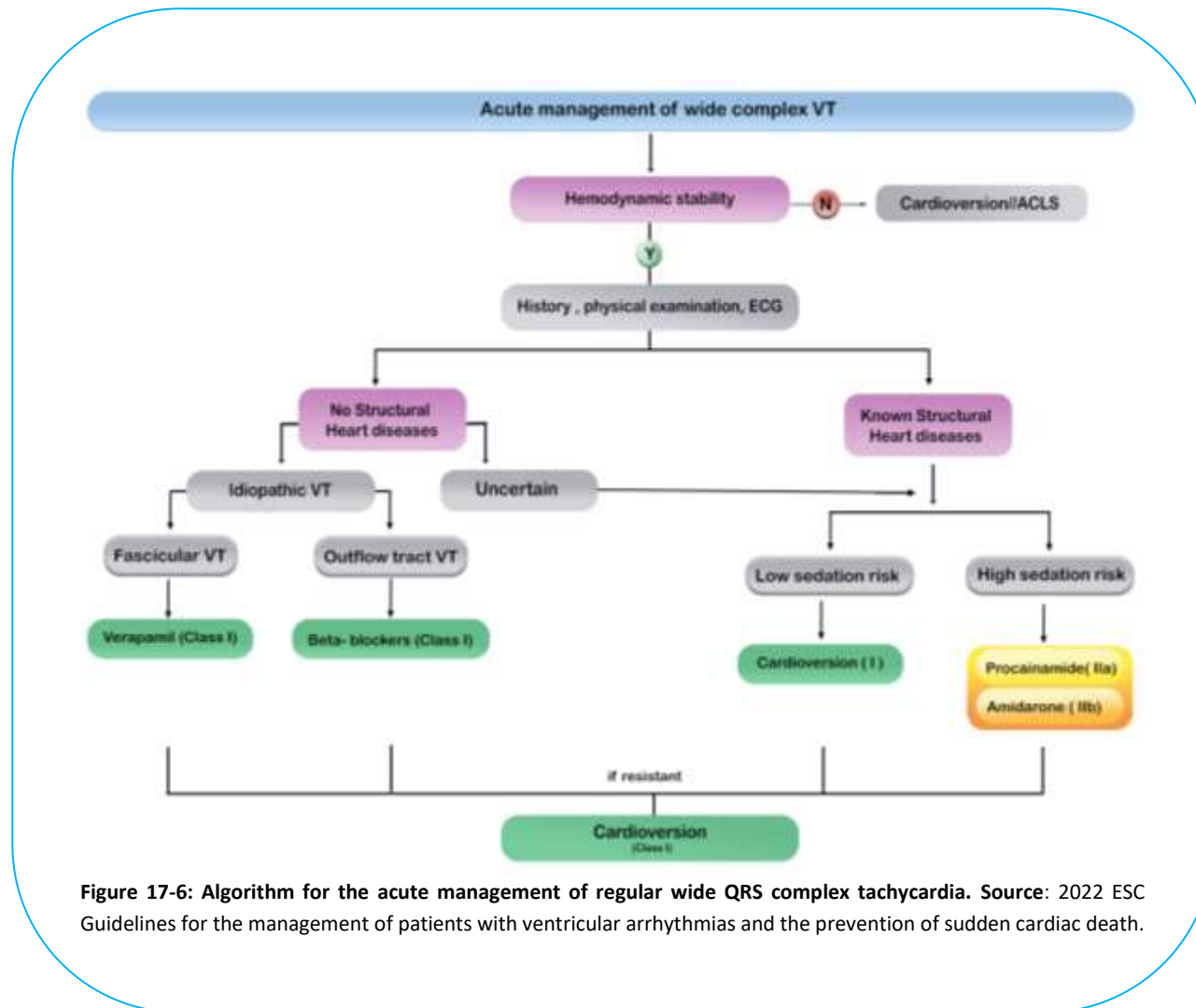


Figure 17-6: Algorithm for the acute management of regular wide QRS complex tachycardia. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-5: ESC Recommendations for acute management of sustained ventricular tachycardia:

Recommendations

DC cardioversion is recommended as the first-line treatment for patients with:

| <i>Class</i> | <i>Level</i> |
|--------------|--------------|
| I | B |

| | | |
|---|-----|---|
| <ul style="list-style-type: none"> - hemodynamically not-tolerated SMVT. - tolerated SMVT provided that the anaesthetic/sedation risk is low. | | |
| <i>In patients presenting with a hemodynamically tolerated idiopathic VT, treatment with intravenous beta-blocker (RVOT VT) or verapamil (fascicular VT) is recommended.</i> | I | C |
| <i>In patients presenting with a regular hemodynamically tolerated wide QRS complex tachycardia suspected for SVT, administration of adenosine or vagal maneuvers should be considered.</i> | IIa | C |
| <i>In patients presenting with a hemodynamically tolerated SMVT and known or suspected SHD, intravenous procainamide should be considered.</i> | IIa | B |
| <i>In patients presenting with a hemodynamically tolerated SMVT in the absence of an established diagnosis, intravenous amiodarone may be considered.</i> | IIb | B |
| <i>In patients presenting with a hemodynamically tolerated SMVT in the absence of significant SHD, flecainide, ajmaline, or sotalol may be considered.</i> | IIb | C |
| <i>Intravenous verapamil is not recommended in broad QRS complex tachycardia of unknown mechanism.</i> | III | B |

▪ **Management of electrical storm and incessant VT:**

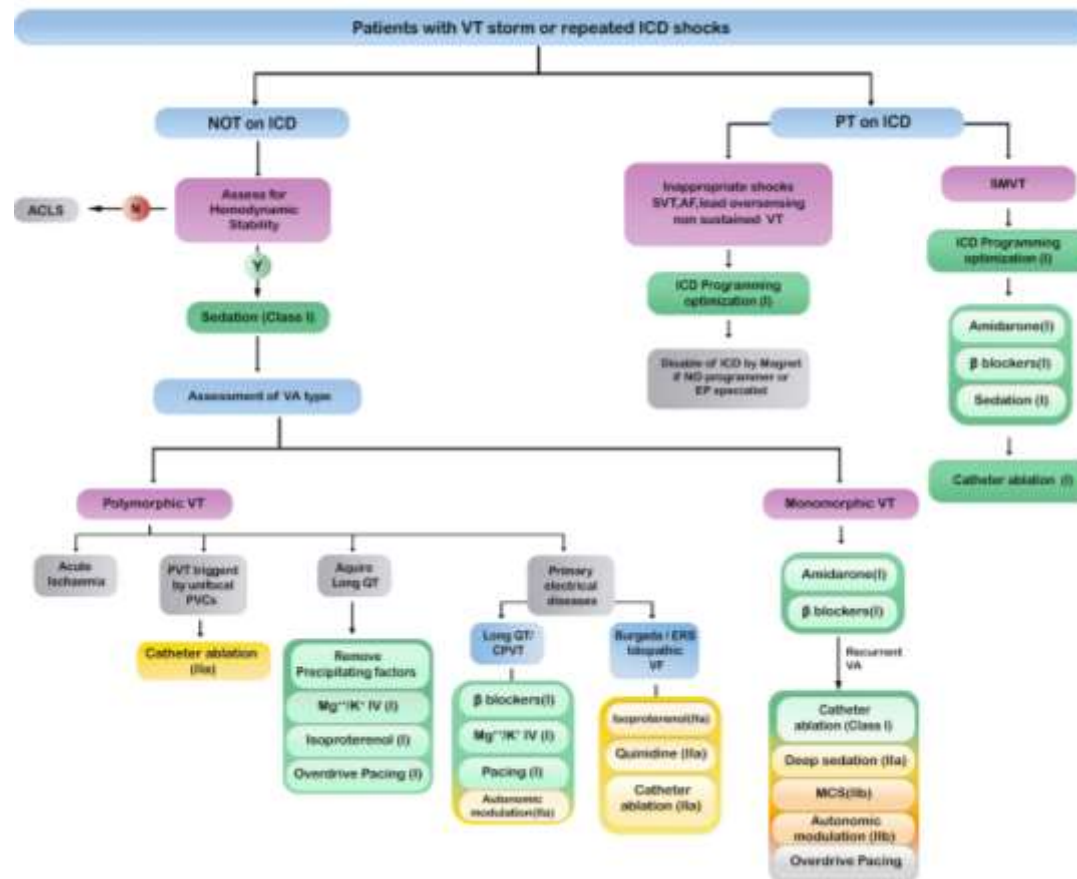


Figure 17-7: Management of patients with electrical storm or repeated ICD discharges. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-6: ESC Recommendations for management of electrical storm:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Mild to moderate sedation is recommended in patients with electrical storm to alleviate psychological distress and reduce sympathetic tone.</i> | I | C |
| <i>Antiarrhythmic therapy with beta-blockers (non-selective preferred) in combination with i.v amiodarone is recommended in patients with SHD and electrical storm unless contraindicated.</i> | I | B |
| <i>I.V magnesium with supplementation of potassium is recommended in patients with TdP.</i> | I | C |
| <i>Isoproterenol ⁽¹⁾ or transvenous pacing to increase heart rate is recommended in patients with acquired LQT syndrome and recurrent TdP despite correction of precipitating conditions and magnesium.</i> | I | C |
| Catheter ablation | | |
| <i>- is recommended in patients presenting with electrical storm due to SMVT refractory to AADs.</i> | I | B |
| <i>- should be considered in patients with recurrent episodes of PVT/VF triggered by a similar PVC, non-responsive to medical treatment or coronary revascularization.</i> | IIa | C |
| <i>Deep sedation/intubation should be considered in patients with an intractable electrical storm refractory to drug treatment.</i> | IIa | C |
| <i>Quinidine may be considered in patients with CAD and electrical storm due to recurrent PVT when other AAD therapy fails.</i> | IIb | C |

(1) When VT/VF recurs despite antiarrhythmic drugs and sedation and the resting sinus rate is relatively slow, consider that VT/ VF is actually triggered or accentuated by the low catecholaminergic tone (e.g., Brugada syndrome, early repolarization VF, pause- induced VT or torsades, short QT syndrome). In those cases, isoproterenol is the solution (+/- quinidine for Brugada and early repolarization VF), not β -blockers or sedation.

| | | |
|--|------------|----------|
| <i>Autonomic modulation (i.e., percutaneous ganglionic stellate blockade, thoracic epidural anaesthesia, or left cardiac sympathetic denervation) may be considered in patients with electrical storm refractory to drug treatment and in whom catheter ablation is ineffective or not possible.</i> | IIb | C |
| <i>Institution of mechanical circulatory support may be considered in the management of drug-refractory electrical storm and cardiogenic shock ⁽¹⁾.</i> | IIb | C |

Long-term management of VA:

- **Pharmacotherapy:** Until now, no AAD except for beta-blockers has demonstrated reduction in all-cause mortality. Chronic antiarrhythmic therapy (mainly amiodarone or sotalol) is indicated in patients who already have an ICD but continue to have frequent, recurrent VT. Antiarrhythmic drugs are used to prevent symptoms and frequent shocks; they do not clearly reduce mortality.

The pro-arrhythmic effects of sodium channel blocking agents and QT prolonging drugs are related to ECG changes. Therefore, follow-up with periodic ECG and additional tests can be required depending on AAD characteristics and patient profile.

(1) *Institution of mechanical circulatory support may be considered for haemodynamic stabilization, when conventional therapy fails, and to provide circulatory support during ablation (Prophylactic –rather than rescue- use of mechanical circulatory support during ablation is associated with lower mortality).*

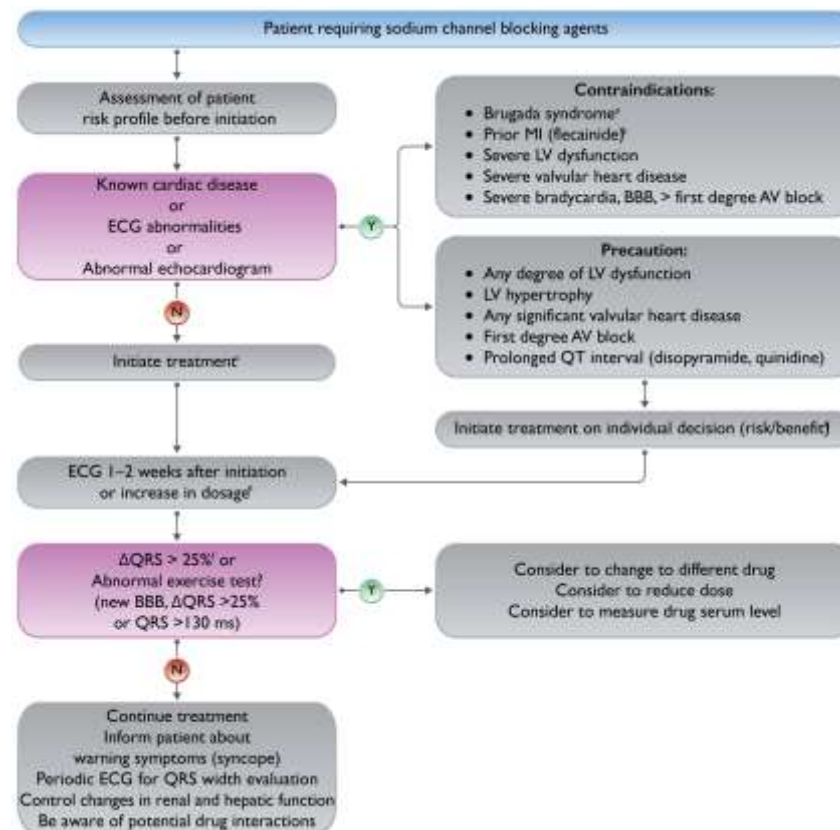


Figure 17-8: Algorithm for evaluation before initiation and follow-up of patients requiring sodium channel blocking agents. (A) <http://www.brugadadrugs.org>. (B) Flecainide, encainide. (C) Co-administration of drugs with AV nodal blocking effect in patients with atrial fibrillation or atrial flutter. (D) In implantable cardioverter defibrillator carriers, a higher risk of drug-induced pro-arrhythmia might be accepted. (E) According to the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. (F) A $\Delta\text{QRS} > 25\%$ is not an absolute cut-off value but dependent on QRS width before drug initiation and individualized patient risk-benefit considerations. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

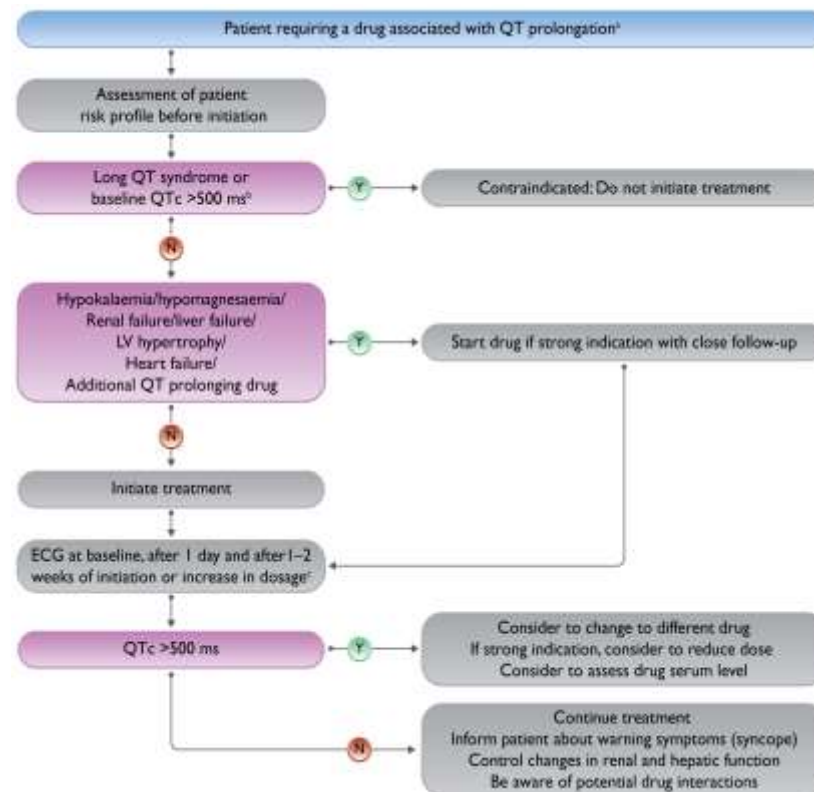


Figure 17-9: Algorithm for evaluation before initiation and follow-up of patients requiring drugs associated with QT prolongation. (A) <http://www.crediblemeds.org>. (B) If strong indication and no alternative treatment, consult a specialist. (C) According to the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

- **Device therapy (ICD):** *Discussed in chapter: cardiac pacing*

- **For secondary prevention of SCD:** the use of ICD demonstrated a 28% mortality reduction, so ICD implantation is indicated after any sustained VT, except in the following three cases:
 1. Polymorphic VT occurring during acute ischemia that eventually gets treated with revascularization ⁽¹⁾.
 2. Polymorphic VT/VF occurring within the first 48 hours of a STEMI.
 3. Idiopathic monomorphic VT with no structural heart disease and no primary electrical disorders.
- **For primary prevention of SCD:** Several RCTs have established the role of the ICD for primary prevention of SCD in heart failure patients with an LVEF $\leq 35\%$. In the work-up for ICD therapy, it is of paramount importance to consider the patient's life expectancy, quality of life, and comorbidities. There is evidence that patients with end-stage renal disease, with diabetes, and elderly patients benefit less or not at all from a primary prevention ICD.
- **Catheter ablation:**
 - **Patients with structural heart disease:**
 - In patients with SHD, SMVTs are primarily due to a scar-related re-entrant mechanism.
 - Because of a higher risk of SCD, an ICD implantation is usually recommended in patients with sustained VAs associated with SHD. However, ICDs do not prevent VA.
 - For patients who continue to have recurrent ICD shocks from scar-related VT despite amiodarone, VANISH trial showed that VT catheter ablation reduces recurrent events by ~45% compared to antiarrhythmic escalation (increasing amiodarone to 300 mg/day and adding mexiletine).
 - The critical part of re-entrant VT circuits, referred to as the 'protected VT isthmus', is the primary target for ablation, but it is very challenging to unmask in hemodynamically not-tolerated VT.

(1) *In that respect, monomorphic VT should not be considered as solely due to transient ischemic episodes, and revascularization of a lesion producing ischemia is not enough to prevent VT/VF. Rather than a purely reversible ischemia, an underlying irreversible scar is probably present. Also note that VT, by itself, often leads to low-level troponin elevation. As stated in the ACC guidelines, "Sustained monomorphic VT with prior MI is unlikely to be affected by revascularization."*

- The electrophysiological characteristics of VT circuits depend on the underlying SHD. In post-infarct VTs are mainly related to an endocardial VT circuit (amenable to endocardial ablation), but intramural and/or epicardial involvement are more common in patients with cardiomyopathies.
- When planning VT ablation, it is important to collect all available information about the arrhythmogenic substrate, especially to identify scars (using CMR), and to help determine the exit site of VAs with the 12-lead ECG documentation of clinical VTs or PVCs that induce PVT/VF.
- The mean long-term success rate of VT ablation varies from 30% to 70%, depending on the underlying SHD. Peri-procedural complications, in particular stroke, cardiac tamponade, or death, may occur.
- **Patients without apparent structural heart disease:**
 - 'Idiopathic VTs' is the term for VTs that are not associated with SHD or a genetic arrhythmic syndrome.
 - Most idiopathic VTs are mediated by triggered activity, but a re-entrant mechanism (involving the LV Purkinje network) explains verapamil-sensitive fascicular VTs.
 - The earliest site of activation during VT is the ablation target for focal sources, while abnormal Purkinje tissue (with diastolic activity during VT) is the ablation target of left fascicular VTs.
 - Ablation is recommended as the first-line therapy for RVOT and fascicular PVCs/VT. The available information for other forms of idiopathic PVCs/VT is limited (lower success, more recurrences and more complications at specific locations e.g. sinus of Valsalva, LV summit ⁽¹⁾).
 - Ablation should be deferred in young and small children due to the risk of complications and the relatively larger size of the ablation lesion.
- **Autonomic modulation:**
 - Sympathetic activation has been demonstrated as playing a key role in inducing VAs in some entities, such as congenital LQTS and CPVT.

(1) LV summit is a triangular area at the most superior portion of the left epicardial ventricular region, surrounded by the two branches of the left coronary artery: LAD and LCx.

- The efficacy of cardiac sympathetic blockade by different approaches (thoracic epidural anesthesia, percutaneous stellate ganglion anesthesia, or surgical stellate ganglion resection) in reducing the arrhythmia burden in refractory VT/VF has been recognized in several small observational studies.

Management of VA according to disease on presentation:

I. Idiopathic PVCs/VT

- **Idiopathic PVCs/VT:** PVCs/VT in patients without SHD are defined as idiopathic. These VTs are **benign** as they do not lead to sudden death. They account for ~10% of all VT referral cases.
- Three important key features distinguish idiopathic VTs from VTs associated with SHD:
 1. Idiopathic VTs mostly originate from a single site and specific region of the heart (namely the RVOT or LVOT, along the valve annuli, papillary muscle, or the LV Purkinje network).
 2. No detectable scar is found in idiopathic VTs.
 3. Idiopathic VTs have a benign prognosis, so that ICD implantation is generally not recommended.
- **Origin:** It may arise from: the RVOT, LVOT or its myocardial extension to an aortic sinus; or from the left posterior fascicle (posterior septum, near the apex), or rarely the left anterior fascicle.
- **Manifestation:**
 - Idiopathic PVCs and VTs frequently present as palpitations and dizziness, usually in young patients (< 50 years old); syncope is rare and sudden death is very rare.
 - RVOT VT and LVOT VT most commonly (60-90%) manifest as repetitive, NSVT that may occur with exertion, stress, or rest.
 - Fascicular VT manifest as sustained VT typically occurs at rest but may be triggered with stress, occasionally leading to a tachycardia-mediated cardiomyopathy.
- **ECG features:** These VTs have specific ECG features (during VT, not during sinus rhythm):
 - **RVOT VT:** LBBB with vertical, almost right axis, looking toward the inferior leads. ARVD-associated VT may mimic RVOT VT.

- **LVOT VT:** RBBB with vertical axis; or LBBB with vertical axis (particularly right cusp VT), but R transition in V2, earlier than RVOT VT.
- **Fascicular VT** (Belhassen): RBBB with LAFB. Since it originates near the normal conduction system, QRS is relatively narrow (~140 ms). Therefore, this VT is difficult to differentiate from SVT.
- RVOT VT and LVOT VT represent cAMP-mediated triggered activity, and therefore may acutely resolve with adenosine. LV fascicular VT represents reentry across abnormally oriented posterior fascicular Purkinje fibers and only rarely responds to adenosine or β -blockers.
- **Therapy** includes verapamil (effective in all idiopathic VTs) or β -blockers (more in outflow tract VT), or catheter ablation of the PVC/VT focus. Flecainide and sotalol are more effective for VT and frequent PVCs. ICD is not indicated, as these VTs do not lead to sudden death.

N.B:

- ARVD does not respond to adenosine, and thus the response to adenosine helps differentiate RVOT VT from ARVD.
- Do not confuse idiopathic VTs with bundle branch reentrant tachycardia; the latter is a very malignant and fast VT occurring in patients with cardiomyopathy and scar tissue across the Purkinje system (bundle branches). It may also be seen after valvular surgery damaging Purkinje system, or TAVR. Unlike idiopathic VT, baseline QRS conduction delay is present. The circuit is a macro-reentry with down conduction across the right bundle, and up conduction across the left bundle, leading to a typical LBBB morphology.

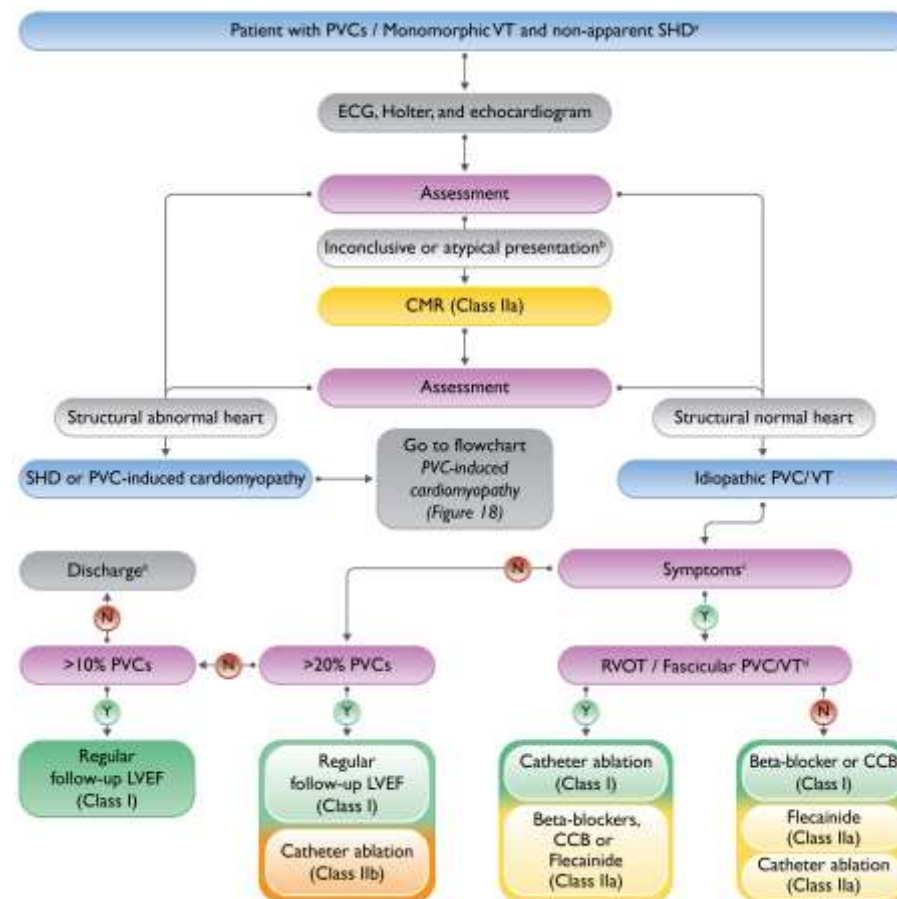


Figure 17-10: Algorithm for the management of patients with idiopathic PVCs/VT and non-apparent structural heart disease. (A) Non-apparent SHD is defined by lack of significant abnormalities in physical examination, basal ECG, and echocardiogram. **(B)** Atypical presentation: e.g. older age, RBBB morphology, sustained monomorphic VT consistent with re-entry. **(C)** Symptoms should be relevant and related to PVC/VT. **(D)** Origin suspected by ECG or confirmed during electrophysiological evaluation. **(E)** Consider re-evaluation in case of new symptoms or changes in patient clinical condition. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

| Table 17-7: ESC Recommendations for management of patients with idiopathic PVCs/VT: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| General recommendations: | | |
| Regular assessment of ventricular function of patients with PVC burden > 10% and normal ventricular function is indicated. | I | C |
| In patients with PVCs/VT and a presentation not typical for an idiopathic origin ⁽¹⁾ , CMR should be considered, despite a normal echocardiogram. | IIa | C |
| Treatment: | | |
| Catheter ablation as first-line treatment is recommended for symptomatic idiopathic VT/PVCs from the RVOT or the left fascicles ⁽²⁾ . | I | B |
| Beta-blockers or non-dihydropyridine CCBs are indicated in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles. | I | C |
| Beta-blockers, non-dihydropyridine CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is particularly risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles. | IIa | B |
| Catheter ablation or flecainide should be considered in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles. | IIa | C |
| Catheter ablation may be considered for idiopathic VT/PVCs in asymptomatic patients with repeatedly more than 20% of PVCs per day at follow-up. | IIb | B |

(1) Including but not limited to older age, RBBB morphology, SMVT consistent with re-entry.

(2) Level of evidence C for VT/PVCs from left fascicles.

| | | |
|--|------------|----------|
| <i>Catheter ablation of idiopathic VT/PVCs is not recommended in children < 5 years of age or < 10 kg weight except when previous medical therapy fails or when VT is not hemodynamically tolerated.</i> | III | C |
| <i>Amiodarone as a first-line treatment is not recommended in patients with idiopathic VTs/ PVCs.</i> | III | C |
| <i>Verapamil is not recommended in children < 1 year of age with PVC/VT, particularly if they have signs of heart failure or concurrent use of other AADs.</i> | III | C |

Table 17-8: Summary of the recommendations for the treatment of patients with frequent idiopathic PVCs/VT or PVC-induced cardiomyopathy:

| | Ablation | Beta-blocker | CCB | Flecainide | Amiodarone |
|--|-----------------|---------------------|------------|-------------------|-------------------|
| Symptomatic, normal LV function: | | | | | |
| •RVOT/fascicular PVC/VT: | I | IIa | IIa | IIa | III |
| •PVC/VT other than RVOT/fascicular | IIa | I | I | IIa | III |
| LV dysfunction: | | | | | |
| •RVOT/fascicular PVC/VT: | I | IIa | III | IIa | IIa |
| •PVC/VT other than RVOT/fascicular: | I | IIa | III | IIa | IIa |
| PVC Burden > 20%, asymptomatic, normal LV function | IIb | | | | III |

▪ **PVC-induced/-aggravated cardiomyopathy:**

- The patient's medical and family history, 12-lead ECG, Holter-ECG, and echocardiography form the cornerstones of the evaluation of patients with suspected PVC-induced cardiomyopathy.

- PVC burden is the strongest independent predictor of PVC-induced cardiomyopathy. Day-by-day fluctuations of PVC burden have been reported in patients undergoing 14-day monitoring. A PVC burden of at least 10% appears to be the minimal threshold for development of PVC-induced cardiomyopathy, and the risk increases with PVC burden > 20%.
- Factors predicting adverse LV remodelling in patients with frequent PVCs include:
Superior PVC axis, Epicardial origin, NSVT, Shorter coupling interval, and Male gender.
- Frequent PVCs can also aggravate LV dysfunction in patients with SHD. In such cases, LV dysfunction can either be a direct consequence of PVCs as in PVC-induced cardiomyopathy, or due to the limiting effect of PVCs on optimal biventricular pacing in CRT patients.
- The following parameters suggest PVC-induced cardiomyopathy (vs PVC-aggravated Cardiomyopathy):
 - Shorter intrinsic QRS duration.
 - Smaller LV end diastolic diameter.
 - Absence of LGE on CMR (Presence of LGE suggests SHD with frequent PVCs).
 - LVEF improvement/normalization (reverse remodelling) following suppression of the PVCs.
- Catheter ablation of the PVCs is considered first-line treatment for PVC-induced cardiomyopathy, with reported success rates of 75-90%.
- Factors affecting acute ablation success and clinical outcome include the site of origin of PVCs (highest for outflow tract PVCs), the number of PVC morphologies, and the absence of LGE on CMR.

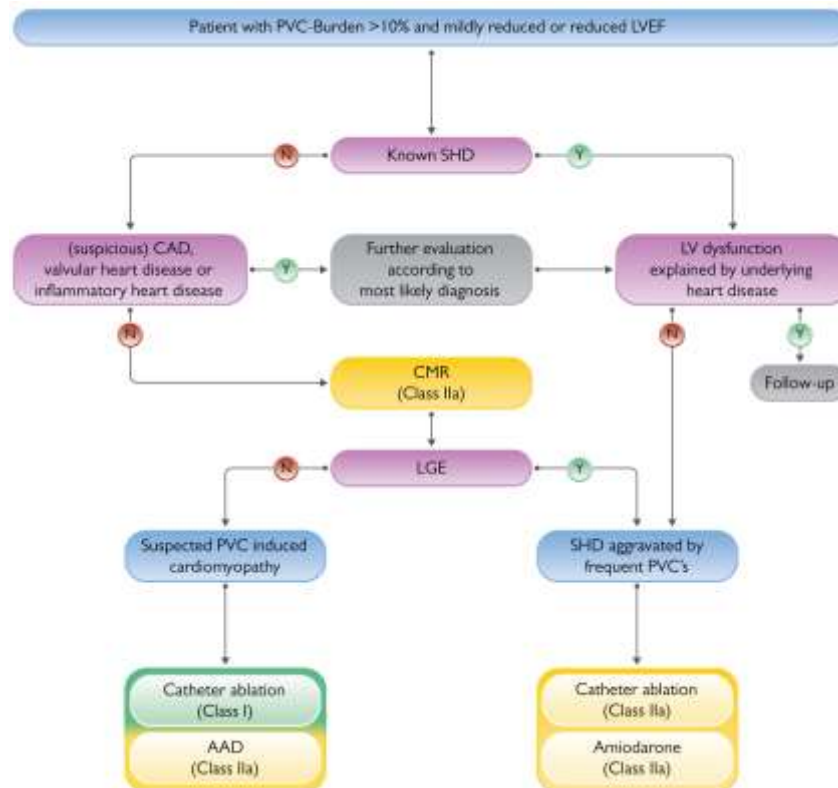


Figure 17-11: Algorithm for the management of patients with PVC-induced/-aggravated cardiomyopathy. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-9: ESC Recommendations for management of patients with PVC-induced or PVC-aggravated cardiomyopathy:

| Recommendations | Class | Level |
|-------------------------------|-------|-------|
| Diagnostic evaluation: | | |

| | | |
|--|------------|----------|
| <i>In patients with an unexplained reduced EF and a PVC burden of at least 10%, PVC-induced cardiomyopathy should be considered.</i> | Ila | C |
| <i>In patients with suspected PVC-induced cardiomyopathy, CMR should be considered.</i> | Ila | B |
| Treatment: | | |
| <i>In patients with a cardiomyopathy suspected to be caused by frequent and predominately monomorphic PVCs, catheter ablation is recommended.</i> | I | C |
| <i>In patients with a cardiomyopathy suspected to be caused by frequent and predominately monomorphic PVCs, treatment with AADs ⁽¹⁾ should be considered if catheter ablation is not desired, suspected to be high-risk, or unsuccessful.</i> | Ila | C |
| <i>In patients with SHD in whom predominately monomorphic frequent PVCs are suspected to be contributing to the cardiomyopathy, AAD (amiodarone) treatment or catheter ablation should be considered.</i> | Ila | B |
| <i>In non-responders to CRT with frequent, predominately monomorphic PVCs limiting optimal biventricular pacing despite pharmacological therapy, catheter ablation or AADs should be considered.</i> | Ila | C |

II. Primary electrical Disease

Table 17-10: Primary Electrical Diseases (Ion Channel Diseases):

I. Cell membrane ion channelopathies:

A. Sodium channel diseases:

Brugada syndrome (I_{Na}): loss of function

Long QT-3 syndrome (I_{Na}): gain of function

(1) Flecainide only in selected patients (ICD recipients, only moderate LV dysfunction).

| |
|---|
| Lenegre-Lev disease (I_{Na}): loss of function ⁽¹⁾ |
| B. Potassium channel diseases: |
| Long QT-1 syndrome (I_{Ks}) |
| Long QT-2 syndrome (I_{Kr}) |
| Long QT-5 syndrome (I_{Ks}) |
| Long QT-6 syndrome (I_{Kr}) |
| Long QT-7 syndrome (I_{K1}) = Andersen-Tawil syndrome Type 1 |
| II. Sarcoplasmic reticulum ion channelopathies: |
| Calcium-release channel disease |
| Catecholaminergic polymorphic ventricular tachycardia (RyR2) |
| III. Possible ion channelopathies of unknown ion channels: |
| Long QT-4 syndrome |
| Short QT syndrome |
| Idiopathic ventricular fibrillation |

Three general mechanisms responsible for arrhythmia susceptibility have been elucidated in these disorders: abnormal repolarization (e.g., LQTS, SQTS, BrS), slow ventricular conduction (e.g., BrS), and aberrant intracellular Ca^{2+} homeostasis (e.g., CPVT).

- **Brugada syndrome (BrS):**

- **Diagnosis:**

1) *Lenègre or Lev's disease is progressive cardiac conduction disease, characterized by an age-related alteration in the conduction of the cardiac impulse that can ultimately lead to chronic AV block, justifying pacemaker implantation. In 1999, a splicing mutation was identified in the SCN5A gene in a French family, resulting in nonfunctional cardiac sodium channels and leading to hereditary Lenègre disease. It was therefore likely that a combination between the SCN5A mutation and degenerative abnormalities in relation with aging explains the progressive alteration of the conduction velocity in hereditary Lenègre patients.*

BrS is rare autosomal dominant condition due to sodium channel (SCN5A) gene mutation with loss of function, predominantly at the level of the epicardial RVOT, creating the ECG abnormalities in V₁-V₃. It is mainly expressed in men (90% of patients).

There are three types of Brugada patterns:

- Type 1: coved ST elevation ≥ 2 mm at the J point, with T-wave inversion in at least one right precordial ECG lead, V₁ or V₂, positioned in the second, third or fourth intercostal spaces.
- Type 2: saddleback ST elevation ≥ 1 mm with upright or biphasic T wave
- Type 3: coved ST < 2 mm or saddleback ST < 1 mm

The spontaneous type 1 Brugada pattern is the only one specifically associated with sudden death and most specifically called Brugada syndrome. The other two patterns are suspicious patterns but may be seen in healthy individuals; they require provocative testing with class I drugs for confirmation.

The type 1 Brugada ECG pattern may occur either spontaneously or be induced by fever or exposure to sodium channel blocking drugs ⁽¹⁾.

Diagnosis of BrS in the induced type 1 ECG pattern requires other clinical features such as documented PVT/VF, arrhythmic syncope, or relevant family history.

BrS leads to polymorphic VT or VF, not monomorphic VT. The arrhythmia often occurs during sleep, or after triggers, such as fever or anesthesia.

It is mandatory to exclude other conditions that may explain the type 1 pattern, so-called phenocopies.

The yield of genetic testing in BrS patients is approximately 20%, with the SCN5A gene is the only gene.

○ **Management:**

ICD implantation is indicated in symptomatic BrS patients who are survivors of CA or have documented spontaneous sustained VA and arrhythmic syncope.

In case of recurrent ICD shocks for VF, quinidine or catheter ablation have been successful in reducing shock frequency, but ablation in asymptomatic patients is not recommended. Isoproterenol infusion can suppress electrical storm.

(1) Na channel blockers, such as flecainide or procainamide (class I AAD), cocaine, anesthesia (propofol, lidocaine), or tricyclic drugs.

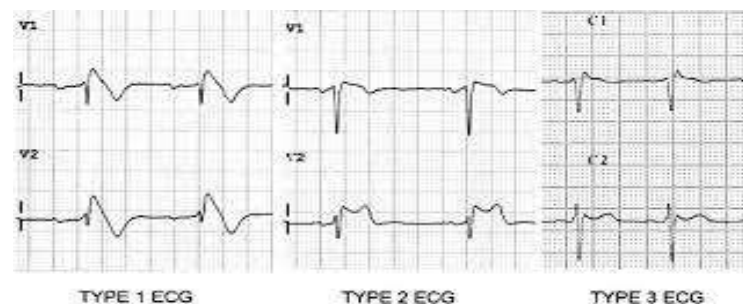


Figure 17-12: ECG Brugada patterns. Source: <https://litfl.com/brugada-syndrome-ecg-library/>

Table 17-11: ESC Recommendations for management of patients with Brugada syndrome:

| Recommendations | Class | Level |
|--|-------|-------|
| Diagnosis: | | |
| It is recommended that BrS is diagnosed in patients with no other heart disease and: <ul style="list-style-type: none"> - a spontaneous type 1 Brugada ECG pattern. - who have survived a CA due to VF or PVT and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever. | I | C |
| BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of: <ul style="list-style-type: none"> - Arrhythmic syncope or nocturnal agonal respiration - A family history of BrS - A family history of SD (< 45 years old) with a negative autopsy and circumstance suspicious for BrS. | IIa | C |
| Genetic testing for SCN5A gene is recommended for probands with BrS. | I | C |
| BrS may be considered as a diagnosis in patients with no other heart disease who exhibit an induced type 1 Brugada ECG. | IIb | C |

| | | |
|---|------------|----------|
| <i>Sodium channel blocker test is not recommended in patients with a prior type I Brugada pattern.</i> | III | C |
| General recommendations: | | |
| <i>The following is recommended in all patients with BrS:</i> | I | C |
| <i>(a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org).</i> | | |
| <i>(b) Avoidance of cocaine, cannabis, and excessive alcohol intake.</i> | | |
| <i>(c) Treatment of fever with antipyretic drugs.</i> | | |
| Risk stratification, prevention of SCD and treatment of VA: | | |
| <i>ICD implantation is recommended in patients with BrS who:</i> | I | C |
| <i>(a) are survivors of an aborted CA and/or</i> | | |
| <i>(b) have documented spontaneous sustained VT.</i> | | |
| <i>ICD implantation should be considered in patients with type 1 Brugada pattern and an arrhythmic syncope.</i> | IIa | C |
| <i>Implantation of a loop recorder should be considered in BrS patients with an unexplained syncope.</i> | IIa | C |
| <i>Quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks.</i> | IIa | C |
| <i>Isoproterenol infusion should be considered in BrS patients suffering electrical storm.</i> | IIa | C |
| <i>Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.</i> | IIa | C |
| <i>PES may be considered in asymptomatic patients with a spontaneous type I BrS ECG.</i> | IIb | B |

| | | |
|--|-----|---|
| ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli. | IIb | C |
| Catheter ablation in asymptomatic BrS patients is not recommended. | III | C |

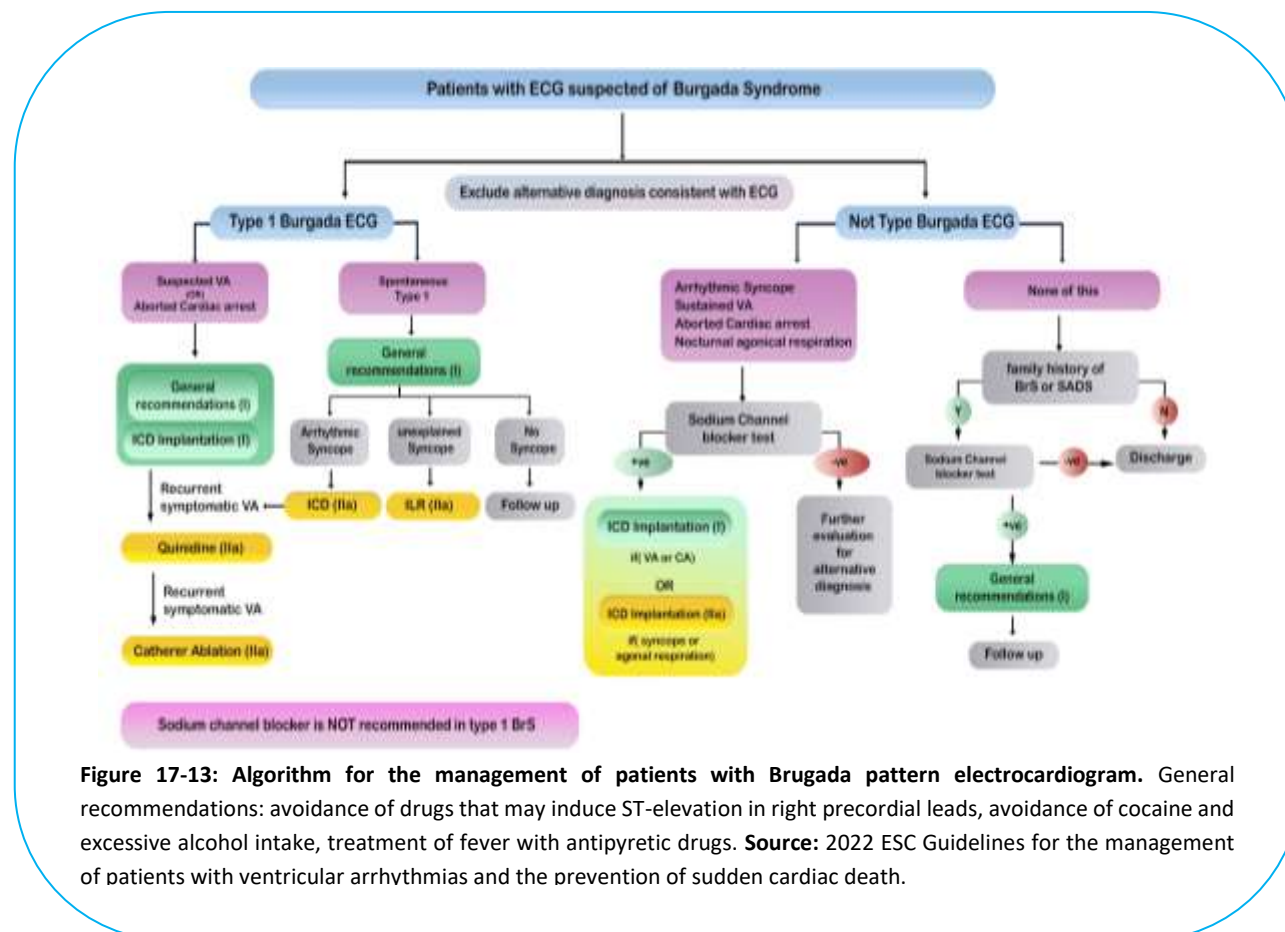


Figure 17-13: Algorithm for the management of patients with Brugada pattern electrocardiogram. General recommendations: avoidance of drugs that may induce ST-elevation in right precordial leads, avoidance of cocaine and excessive alcohol intake, treatment of fever with antipyretic drugs. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

▪ Long QT syndrome:

- LQTS is characterized by a prolonged QT interval and VAs mainly triggered by adrenergic activation.

- The mean age at presentation is 14 years. The annual rate of SCD in asymptomatic patients with untreated LQTS has been estimated to be < 0.5%, while it increases to 5% with history of syncope.
- **The most common LQT syndromes are:**
 - **LQT1** (~35%): caused by KCNQ1 mutation which leads to loss of function of K channels (I_{Ks}). ECG shows long QT with broad and long T wave. TdP in LQT1 is triggered with swimming or physical or emotional stress.
 - **LQT2** (25%): caused by KCNH2 mutation which leads to loss of function of K channels (I_{Kr}). ECG shows long QT with broad and notched T wave. TdP in LQT2 is triggered with sudden noise or emotion as well as postpartum.
 - **LQT3** (~5-10%): caused by SCN5A mutation which leads to gain of function of Na channels leading to increased depolarization and thus prolongation of the plateau phase of repolarization, i.e., prolongation of the ST segment with a normal-width T wave. TdP in LQT3 is triggered with sleep.
- **Diagnosis:**
 - **Diagnostic criteria:** QTc \geq 480 ms (In the presence of arrhythmic syncope or CA, a QTc \geq 460 ms is sufficient to consider a diagnosis of LQTS) or LQTS risk score > 3.
 - QT interval is often best measured in leads II and V₅ or V₆ (leads that shows the best separation of T and U waves). A challenge for the clinician is establishing the duration of the QT interval in patients with broad QRS complexes (e.g., in the presence of ventricular pacing or BBB). In this setting, a formula has been proposed that adjusts QT by QRS duration.
 - While measuring the QT, the patient moving briskly from recumbent to orthostatic position may be helpful for the diagnosis of LQTS.
 - Epinephrine challenge is not recommended as a routine diagnostic tool, as reproducibility is modest.
- **Genetic screening:**
 - Genetic screening identifies a mutation in 75% of cases (the 3 main genes account for 90% of positively genotyped cases).
 - **Subtypes:** The subtypes of LQTS may be grouped as follows:
 1. Autosomal-dominant LQTS without extra-cardiac manifestation (called, Romano-Ward syndrome).
 2. Autosomal-dominant LQTS with extra-cardiac manifestation, comprising:

A. Andersen-Tawil Syndrome (LQT7) increasingly considered its own entity.

B. Timothy Syndrome (LQT8), characterized by prolonged QT, syndactyly, cardiac malformations, autism spectrum disorder and dysmorphism.

3. Autosomal-recessive LQTS (Jervell and Lange-Nielsen Syndrome), combining extreme QT prolongation with congenital deafness.

- Patients with a clinical diagnosis of LQTS are recommended to undergo genetic testing to:

Receive genotype specific management (e.g Mexiletine for LQT3).

Permit identification of relatives at risk (Relatives with a mutation but without QT prolongation still receive a diagnosis of LQTS, as they are at risk of experiencing VA).

o **Management:**

- All LQTS patients should avoid hypokalaemia, QT-prolonging drugs and genotype-specific triggers.
- Beta-blockers are recommended in all LQTS patients, including silent carriers. Non-selective beta-blockers (nadolol and propranolol) have greater efficacy in reducing arrhythmic risk.
- Mexiletine, a class Ib antiarrhythmic, shortens QT and may be considered in all types of LQT when β -blocker is ineffective, particularly LQT3.
- ICD is recommended in survivors of a CA (as they have a high risk of recurrences; 14% within 5 years on).
- Left cardiac sympathetic denervation (LCSD) is recommended for symptomatic patients despite beta blockers when ICD is contraindicated or declined, or for an ICD carrier who experiences multiple shocks while on beta-blockers.

| Table 17-12: Modified long QT syndrome diagnostic score: | | |
|--|-----------------------------|--------|
| Findings | | Points |
| ECG | QTc \geq 480 ms | 3.5 |
| | QTc = 460-479 ms | 2 |
| | QTc = 450-459 ms (in males) | 1 |

| | | |
|-------------------------|--|-----|
| | QTc \geq 480 ms during 4 th min of recovery from exercise stress test | 1 |
| | Torsade de pointes | 2 |
| | T wave alternans | 1 |
| | Notched T wave in 3 leads | 1 |
| | Low heart rate for age | 0.5 |
| Clinical history | Syncope With stress | 2 |
| | Syncope Without stress | 1 |
| Family history | Family member(s) with definite LQTS | 1 |
| | Unexplained SCD at age < 30 years in first-degree family | 0.5 |
| Genetic finding | Pathogenic mutation ⁽¹⁾ | 3.5 |

(1) Patients with long QT syndrome genotype but normal phenotype (normal QTc) have a real risk of sudden death, albeit smaller than patients with prolonged QTc, and should be treated with β -blockers.

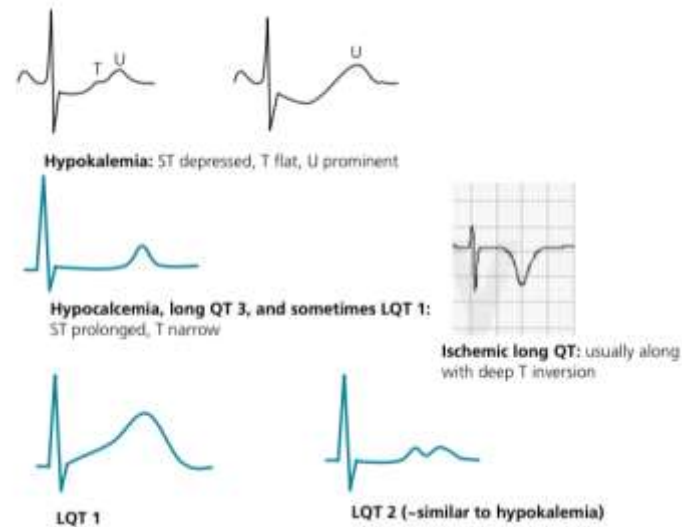


Figure 17-14: Typical ST–T morphologies in hypokalemia, hypocalcemia, and congenital long QT syndromes (LQT). In hypokalemia, ST segment is depressed and U wave is large while T wave is flattened. In hypocalcemia and LQT3, QT interval is prolonged as a result of ST-segment prolongation and, as opposed to other congenital LQT or QT prolongation secondary to drugs, there is no significant widening of the T wave. In LQT1, T wave is wide and ample without ST-segment depression, similar to Figure 9.5. In LQT2, T wave is wide and notched (double hump). LQT1 may have a morphology similar to LQT3 and is actually the most common LQT with this morphology. In all long QT cases, particularly congenital LQT, the T wave may become notched after a pause, the notch representing the early afterdepolarization (EAD) wave that triggers TdP. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

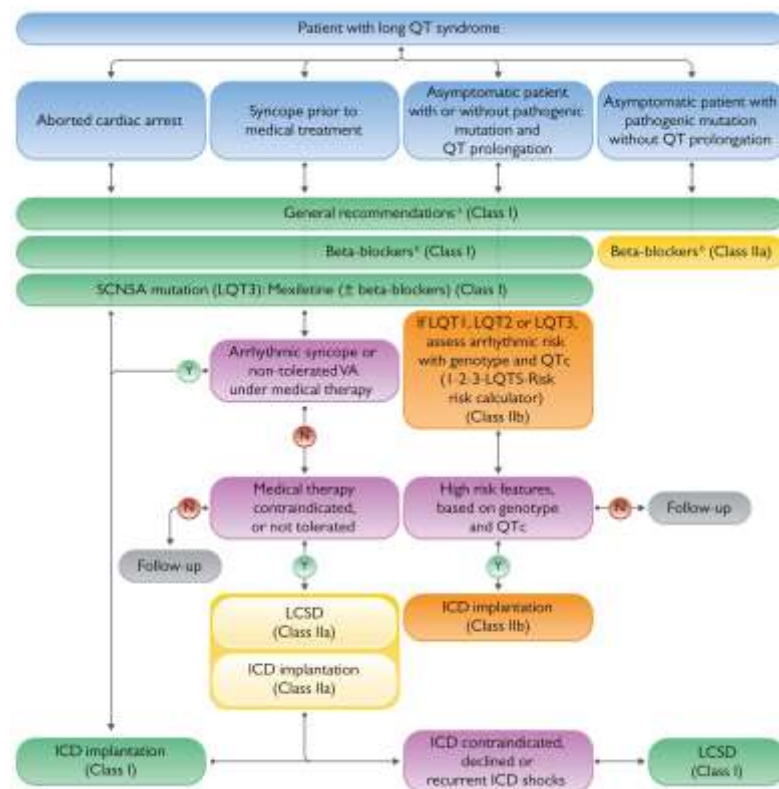


Figure 17-15: Algorithm for the management of patients with long QT syndrome. (A) General recommendations: avoidance of QT-prolonging drugs (<http://www.crediblemeds.org>), correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, and hypocalcaemia), avoidance of genotype-specific triggers for arrhythmias (strenuous swimming in LQT1, exposure to loud noises in LQT2). **(B)** Preferred beta-blockers: nadolol and Propranolol. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-13: ESC Recommendations for management of patients with Long QT syndrome:

Recommendations

Class Level

| | | |
|---|-----|---|
| Diagnosis: | | |
| <i>It is recommended that LQTS is diagnosed with either QTc \geq 480 ms in repeated 12-lead ECGs with or without symptoms <u>or</u> LQTS diagnostic score > 3</i> | I | C |
| <i>The LQTS diagnosis should be considered in the presence of a QTc \geq 460 ms and < 480 ms in repeated 12-lead ECGs in patients with an arrhythmic syncope in the absence of secondary causes for QT prolongation.</i> | IIa | C |
| <i>In patients with clinically diagnosed LQTS, genetic testing and genetic counselling are recommended.</i> | I | C |
| <i>It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration.</i> | I | C |
| <i>Routine diagnostic testing with epinephrine challenge is not recommended in LQTS.</i> | III | C |
| General recommendations to prevent SCD: | | |
| <i>The following is recommended in LQTS:</i> <ul style="list-style-type: none"> - Avoid QT-prolonging drugs. - Avoid and correct electrolyte abnormalities. - Avoid genotype-specific triggers for arrhythmias. | I | C |
| <i>Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol),</i> | | |
| <i>- are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events.</i> | I | B |
| <i>- should be considered in patients with a pathogenic mutation and a normal QTc interval</i> | IIa | B |
| <i>Mexiletine is indicated in LQT3 patients with a prolonged QT interval.</i> | I | C |
| Risk stratification, prevention of SCD and treatment of VA: | | |
| <i>ICD implantation in addition to beta-blockers is recommended in LQTS patients with CA.</i> | I | B |
| <i>ICD implantation is recommended in patients with LQTS who are symptomatic while receiving beta-blockers and genotype-specific therapies (mexiletine in LQT3 patients).</i> | I | C |

| | | |
|--|------------|----------|
| <i>LCSD is indicated in patients with symptomatic LQTS when: (A) ICD therapy is contraindicated or declined; (B) patient is on beta-blockers and genotype-specific drugs with an ICD and experiences multiple shocks or syncope due to VA.</i> | I | C |
| <i>Either ICD implantation or LCSD should be considered in patients with symptomatic LQTS, when beta-blockers and genotype-specific therapies are not tolerated or contraindicated at the therapeutic dose.</i> | IIa | C |
| <i>In LQTS, it should be considered to calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval.</i> | IIa | C |
| <i>ICD implantation may be considered in asymptomatic LQTS patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies.</i> | IIb | B |
| <i>Invasive electrophysiologic study is not recommended in LQTS.</i> | III | C |

▪ **Andersen-Tawil syndrome Type 1:**

Andersen-Tawil syndrome Type 1, also classified as LQT7, is a rare disease characterized by three main symptoms: frequent VA (e.g., bidirectional VT), dysmorphologies and periodic paralysis.

The inward rectifier current (I_{K1}) decreased by **KCNJ2 loss of function mutation** causes an increase in U wave amplitude rather than QT prolongation.

| Table 17-14: ESC Recommendations for management of patients with Andersen-Tawil syndrome: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>Genetic testing is recommended in patients with suspected Andersen-Tawil syndrome.</i> | I | C |
| <i>Andersen-Tawil syndrome should be considered in patients without SHD who present with at least two of the following:</i> | IIa | C |
| <i>- Prominent U waves with or without prolongation of the QT interval</i> | | |

| | | |
|--|-----|---|
| <ul style="list-style-type: none"> - Bidirectional and/or polymorphic PVCs/VT - Dysmorphic features - Periodic paralysis - KCNJ2 pathogenic loss of function mutation. | | |
| Risk stratification, prevention of SCD and treatment of VA: | | |
| ICD implantation is recommended in patients with Andersen-Tawil syndrome after aborted CA or not-tolerated sustained VT. | I | C |
| Beta-blockers and/or flecainide with or without acetazolamide should be considered in patients with Andersen-Tawil syndrome to treat VA. | IIa | C |
| An ILR should be considered in patients with Andersen-Tawil syndrome and unexplained syncope. | IIa | C |
| ICD implantation may be considered in patients with Andersen-Tawil syndrome who have a history of unexplained syncope or suffer from tolerated sustained VT. | IIb | C |

▪ **Catecholaminergic polymorphic ventricular tachycardia:**

- CPVT is a heritable disorder characterized by catecholamine-induced bidirectional VT and PVT in the absence of SHD or ischaemia. The disease has an estimated prevalence of 1 in 10 000.
- There are two main genetic types: **(1)** a dominant disorder due to mutations in the gene encoding for the cardiac ryanodine receptor (RYR2) and **(2)** a recessive disorder caused by mutations in the cardiac calsequestrin gene (CASQ2). Mutations in TRDN and CALM1-3 have been identified in patients with atypical forms of catecholaminergic VAs.
- The clinical manifestations of CPVT usually occur in the first decade of life prompted by physical activity or emotional stress (leads to excessive Ca^{+2} release from the sarcoplasmic reticulum with subsequent delayed afterdepolarization).
- Exercise stress test is the most important diagnostic test, because it elicits the distinguishing bidirectional or PVT that establish the diagnosis.

○ **Treatment:**

- Avoid competitive sports, strenuous exercise, and stressful environments.
- Non-selective beta-blockers such as nadolol and propranolol are preferred. Flecainide significantly reduces the VA burden in CPVT patients and should be considered in addition to beta-blockers when control of arrhythmias is incomplete.
- Maximal protection with beta-blockers, flecainide and ICD is indicated in survivors of a CA.
- Left cardiac sympathetic denervation (LCSD) has been proposed as an additional therapy in patients in whom pharmacological treatment is not effective or feasible.

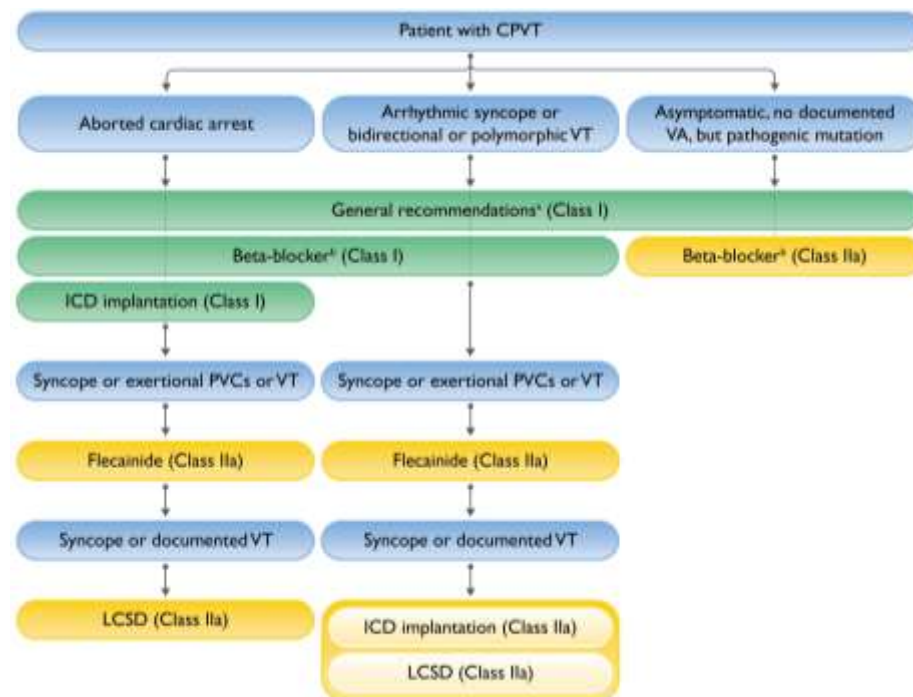


Figure 17-16: Management of patients with catecholaminergic polymorphic ventricular tachycardia. (A) General recommendations: avoidance of competitive sports, avoidance of strenuous exercise, avoidance of stressful environments. **(B)** Preferred beta-blockers: nadolol, propranolol. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-15: ESC recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia:

| Recommendations | Class | Level |
|---|-------|-------|
| Diagnosis: | | |
| <i>It is recommended that CPVT is diagnosed in:</i> | I | C |

| | | |
|---|-----|---|
| <ul style="list-style-type: none"> - Patients with structurally normal heart, normal ECG, and exercise- or emotion-induced bidirectional, or PVT. - Patients who are carriers of a mutation in disease-causing genes. | | |
| Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT. | I | C |
| Epinephrine or isoproterenol challenge may be considered for the diagnosis of CPVT when an exercise test is not possible. | IIb | C |
| General recommendations: | | |
| Avoidance of competitive sports, strenuous exercise, and exposure to stressful environments is recommended in all patients with CPVT. | I | C |
| Therapeutic interventions: | | |
| Beta-blockers, ideally non-selective (nadolol or propranolol) | | |
| <ul style="list-style-type: none"> - are recommended in all patients with a clinical diagnosis of CPVT. - should be considered for genetically positive CPVT patients without phenotype. | I | C |
| | IIa | C |
| Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose. | IIa | C |
| ICD implantation combined with beta-blockers and flecainide is recommended in CPVT patients after aborted CA. | I | C |
| ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide. | IIa | C |
| LCSD should be considered in patients with diagnosis of CPVT when the combination of beta-blockers and flecainide at therapeutic dosage are either not effective, not tolerated, or contraindicated. | IIa | C |
| PES is not recommended for stratification of SCD risk. | III | C |

▪ **Early repolarization syndromes (ERS):**

ERS is diagnosed in a patient resuscitated from PVT or VF without any heart disease and the early repolarization pattern (ERP); J-point elevation ≥ 1 mm in ≥ 2 adjacent inferior and/or lateral ECG leads.

ERP is most often a benign finding. High-risk ECG features have been proposed to increase likelihood of ERS: prominent J-waves ≥ 2 mm, dynamic changes in J-point elevation (> 0.1 mV) and J-waves associated with a horizontal or descending ST-segment.

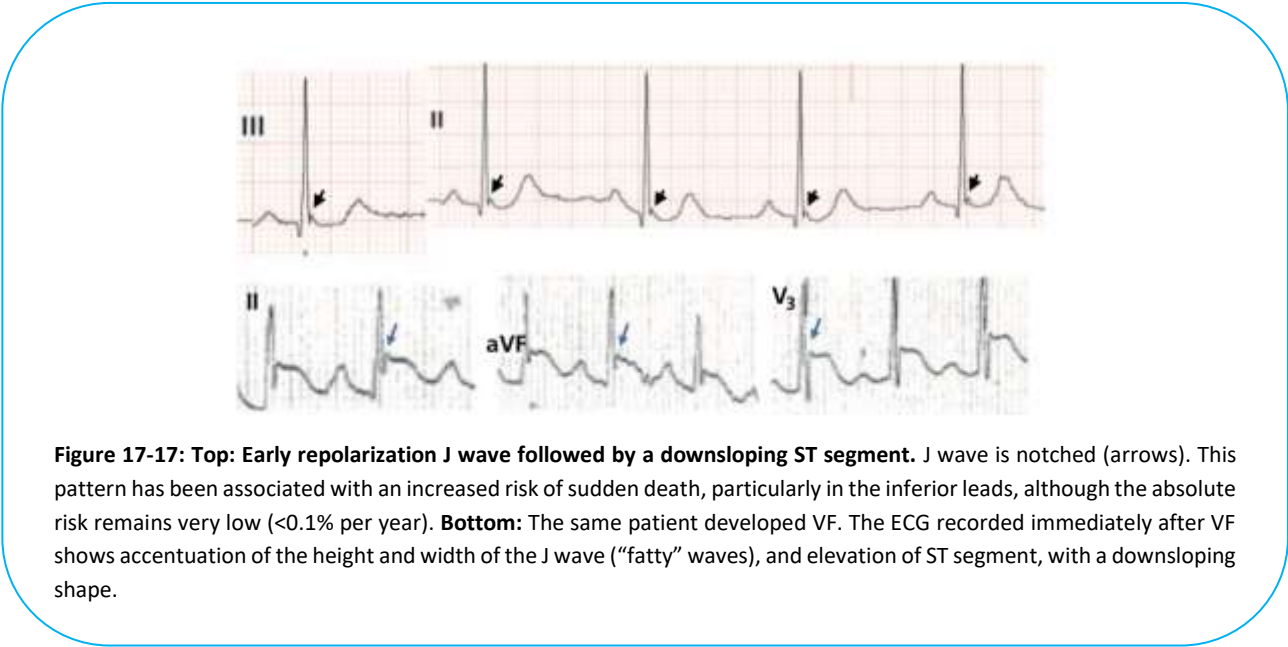


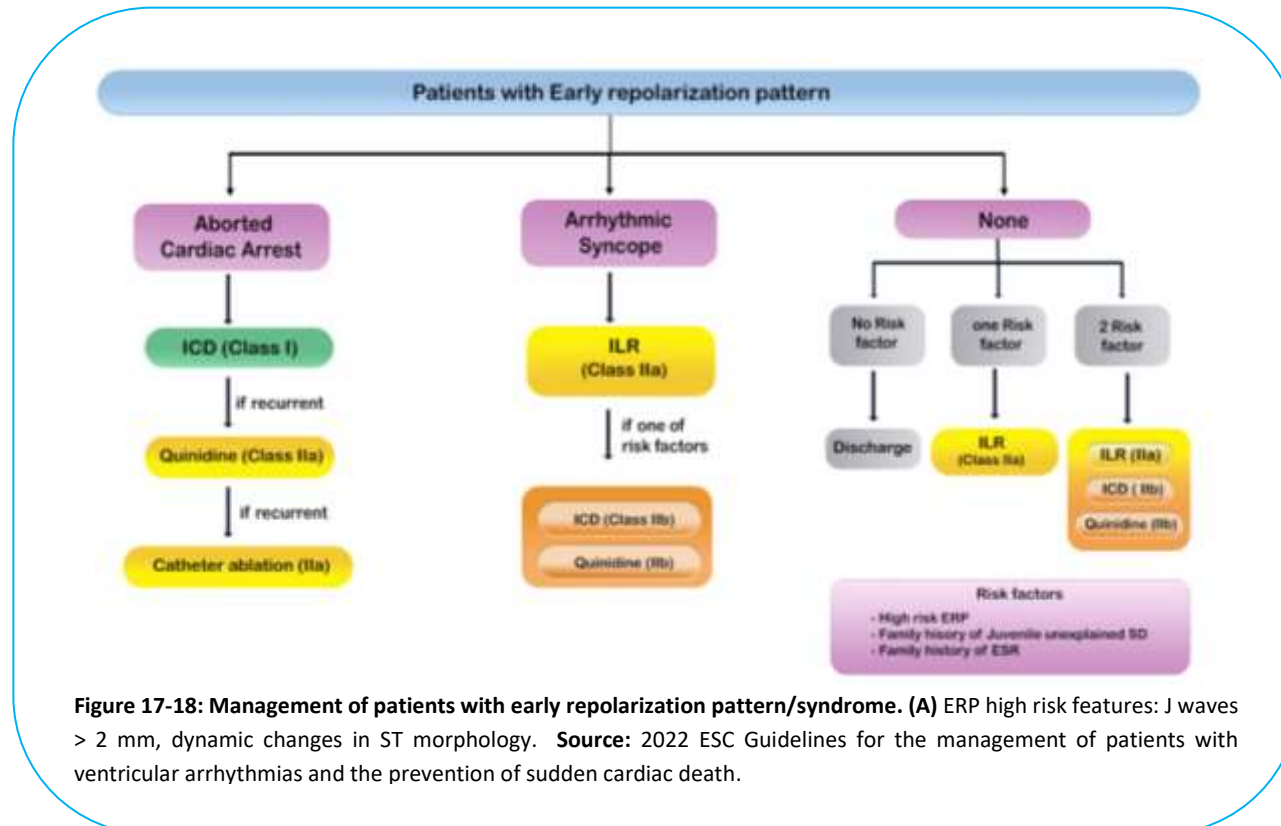
Figure 17-17: Top: Early repolarization J wave followed by a downsloping ST segment. J wave is notched (arrows). This pattern has been associated with an increased risk of sudden death, particularly in the inferior leads, although the absolute risk remains very low (<0.1% per year). **Bottom:** The same patient developed VF. The ECG recorded immediately after VF shows accentuation of the height and width of the J wave (“fatty” waves), and elevation of ST segment, with a downsloping shape.

| Table 17-16: ESC recommendations for the management of early repolarization pattern/syndrome: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| It is recommended that the ERP is diagnosed as J-point elevation of ≥ 1 mm in two adjacent inferior and/or lateral ECG leads. | I | C |
| It is recommended that the ERS is diagnosed in a patient resuscitated from unexplained VF/PVT in the presence of ERP. | I | C |

| | | |
|--|------------|----------|
| <i>In an SCD victim with a negative autopsy and medical chart review, and an ante-mortem ECG demonstrating the ERP, the diagnosis of ERS should be considered.</i> | IIa | C |
| <i>First-degree relatives of ERS patients should be considered for clinical evaluation for ERP with additional high-risk features ⁽¹⁾.</i> | IIa | B |
| <i>Genetic testing in ERS patients may be considered.</i> | IIb | C |
| <i>Clinical evaluation is not recommended routinely in asymptomatic subjects with ERP.</i> | III | C |
| Risk stratification, prevention of SCD and treatment of VA: | | |
| <i>ICD implantation is recommended in patients with a diagnosis of ERS who have survived a CA.</i> | I | B |
| <i>Isoproterenol infusion should be considered for ERS patients with electrical storm.</i> | IIa | B |
| <i>Quinidine in addition to an ICD should be considered for recurrent VF in ERS patients.</i> | IIa | B |
| <i>ILR should be considered in individuals with ERP and at least one risk feature ⁽²⁾ or arrhythmic syncope.</i> | IIa | C |
| <i>PVC ablation should be considered in ERS patients with recurrent VF episodes triggered by a similar PVC non-responsive to medical treatment.</i> | IIa | C |
| <i>ICD implantation or quinidine may be considered in individuals with</i> <ul style="list-style-type: none"> <i>- individuals with ERP and arrhythmic syncope and additional risk features.</i> <i>- asymptomatic individuals who demonstrate a high-risk ERP in the presence of a family history of unexplained juvenile SD</i> | IIb | C |
| <i>ICD implantation is not recommended in asymptomatic patients with an isolated ERP.</i> | III | C |

(1) ERP high-risk features: J waves > 2 mm, dynamic changes in J point and ST morphology.

(2) High-risk ERP: family history of unexplained SD < 40 years, family history of ERS.



▪ Short QT syndrome (SQTs):

- SQTs is a rare genetic disorder characterised by a short QT interval, premature AF and VF in the context of a structurally normal heart.

It has been associated with **gain of function** mutations in KCNQ1, KCNH2 and loss offunction in SLC4A. The disease has high lethality in all age groups, including the first months of life.

- **Management:**

- Quinidine is currently the best supported AAD, but should be monitored for excessive QT prolongation, while isoprenaline may be considered in electrical storm.
- Drugs that shorten QT interval should be avoided, e.g., nicorandil. Loop recorder implantation should be considered in children and young asymptomatic SQTS patients.

Table 17-17: ESC recommendations for the management of patients with short QT syndrome:

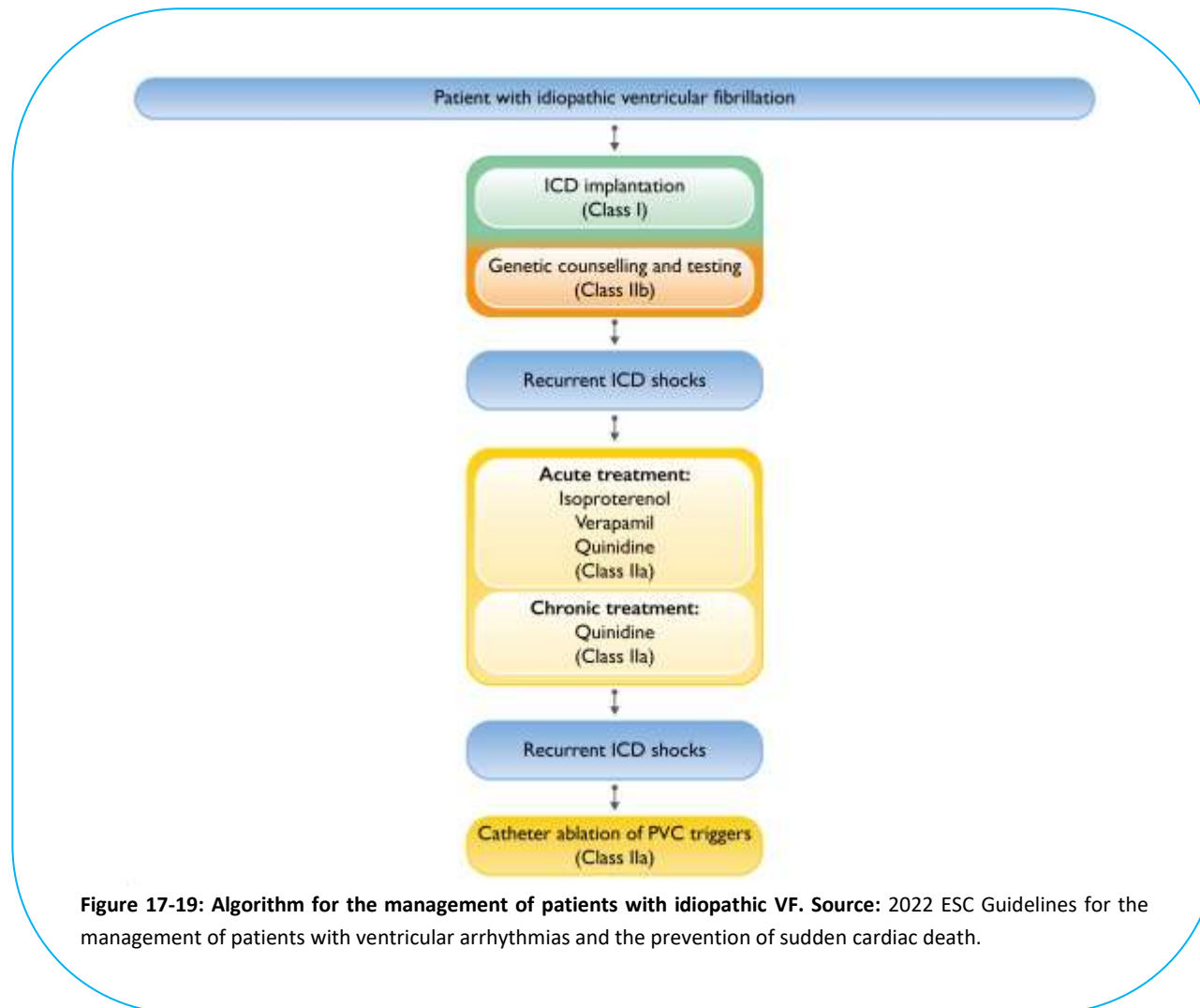
| Recommendations | Class | Level |
|---|-------|-------|
| Diagnosis: | | |
| <i>Genetic testing is indicated in patients diagnosed with SQTS.</i> | I | C |
| <i>SQTS should be considered in the presence of a QTc ≤ 320 ms.</i> | IIa | C |
| <i>It is recommended that SQTS is diagnosed in the presence of a QTc ≤ 360 ms and one or more of the following: (A) pathogenic mutation, (B) family history of SQTS, (C) survival from a VT/VF episode in the absence of heart disease.</i> | I | C |
| <i>SQTS should be considered in the presence of a QTc ≥ 320 ms and ≤ 360 ms and arrhythmic syncope.</i> | IIa | C |
| <i>SQTS may be considered in the presence of a QTc ≥ 320 ms and ≤ 360 ms and a family history of SD at age < 40 years.</i> | IIb | C |
| Risk stratification, SCD prevention and treatment of VA: | | |
| <i>ICD implantation is recommended in patients with a diagnosis of SQTS who: (A) are survivors of an aborted CA and/or (B) have documented spontaneous sustained VT.</i> | I | C |
| <i>ILR should be considered in young SQTS patients.</i> | IIa | C |
| <i>ICD implantation should be considered in SQTS patients with arrhythmic syncope.</i> | IIa | C |
| <i>Quinidine may be considered in: (A) SQTS patients who qualify for an ICD but present a contraindication to the ICD or refuse it, and (B) asymptomatic SQTS patients and a family history of SCD.</i> | IIb | C |
| <i>Isoproterenol may be considered in SQTS patients with an electrical storm.</i> | IIb | C |

▪ **Idiopathic ventricular fibrillation:**

The diagnosis of idiopathic ventricular fibrillation (IVF) is made in SCA survivors, preferably with documented VF, after exclusion of structural, channelopathic, metabolic, or toxicological aetiologies.

In IVF patients, ICD reduces the risk of arrhythmic death by up to 68% compared to amiodarone.

In patients with recurrent episodes of VF triggered by a similar PVC unresponsive to medical treatment, catheter ablation has shown success. PVCs most commonly originate from the Purkinje system and can be eliminated with a high acute success rate of 87-100%.



| Table 17-18: ESC Recommendations for management of patients with idiopathic VF: | | |
|---|-------|-------|
| Recommendations | Class | Level |

| Diagnostic evaluation: | | |
|--|------------|----------|
| <i>It is recommended that idiopathic VF is diagnosed in a SCA survivor, preferably with documentation of VF, after exclusion of an underlying structural, channelopathic, metabolic, or toxicological aetiology.</i> | I | B |
| <i>Clinical testing (history, ECG and high precordial lead ECG, exercise test, echocardiogram) of first-degree family members of idiopathic VF patients may be considered.</i> | IIb | B |
| <i>In idiopathic VF patients, genetic testing of genes related to channelopathy and cardiomyopathy may be considered.</i> | IIb | B |
| Secondary prevention of SCD and treatment of VA: | | |
| <i>ICD implantation is recommended in idiopathic VF.</i> | I | B |
| <i>Isoproterenol infusion, verapamil, or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF.</i> | IIa | C |
| <i>Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF.</i> | IIa | B |
| <i>Catheter ablation by experienced electrophysiologists should be considered in idiopathic VF patients with recurrent episodes of VF triggered by a similar PVC non-responsive to medical treatment.</i> | IIa | C |

Table 17-19: Genetic testing and workup of probands and relatives with primary electrical diseases:

| Idiopathic VF | Long QT syndrome | Brugada syndrome | CPVT | Early Repolarization Syndrome |
|------------------|------------------|------------------|------|-------------------------------|
| Probands: | | | | |

| Genetic testing: | Class IIb | Class I | Class I | Class I | Class IIb |
|------------------------|---|-------------------|---|-------------------|-------------------------|
| Initial clinical test: | | ECG Exercise test | -ECG and high precordial lead ECG -Na channel blocker provocative test | ECG Exercise test | ECG |
| Follow-up | 1-3 years dependent on level of risk | | | | |
| Relatives: | | | | | |
| Clinical screening | - ECG and high precorial lead ECG - ECG Exercise test - Echocardiography | ECG Exercise test | - ECG and high precorial lead ECG: start at 10 years - Na channel blocker provocative test: start at > 16 years unless indicated | | ECG Echocardiography |
| Follow-up | If positive phenotype and/or Class IV/V variant: 1-3 years dependent on level of risk If negative phenotype and no Class IV/V variant: Discharge | | | | |

III. Coronary Artery Diseases

▪ Acute coronary syndromes:

- Early VAs are defined as VT/VF occurring within 48 h after STEMI (occurs in 4-12% of STEMI patients). Early VA have been associated with an up to six-fold increase in in-hospital mortality, whereas long-term prognosis seems not to be significantly affected.
- Predictors of VA in ACS: Hemodynamic instability, cardiogenic shock, LVEF < 40%, early repolarization pattern and the sum of ST-segment deviations in all leads.

- Urgent reperfusion and I.V beta-blocker are recommended to prevent VA in STEMI. Prophylactic treatment with AADs has not proven beneficial, and may even be harmful.
- Patients with life-threatening VAs secondary to coronary vasospasm were at high risk for recurrence. While CCBs are capable of suppressing episodes, beta-blockers may trigger VAs. As medical therapy may not be sufficiently protective, ICD should still be considered in SCA survivors with variant angina.
- **Early after myocardial infarction:**

The first weeks after STEMI carry the highest risk for both all cause death and SCD, particularly in patients with reduced LVEF. Early routine prophylactic ICD implantation in the first 40 days after MI did not reduce mortality in post-MI patients with reduced LVEF (DINAMIT and IRIS trials).
- Early assessment by further non-invasive tests, apart from LVEF measurement, has also not proven to be useful for risk stratification with regard to SCD.

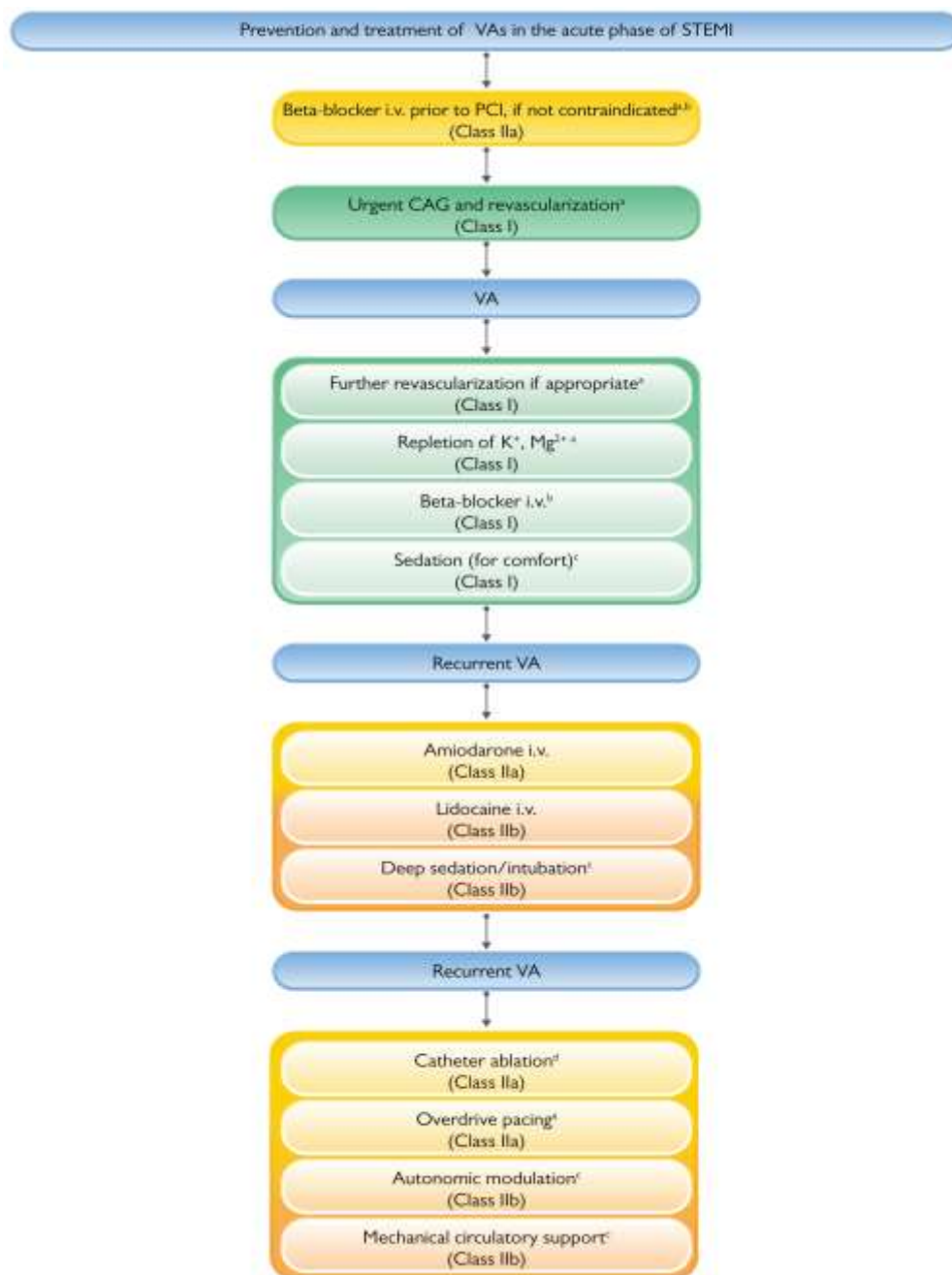


Figure 17-20: Prevention and management of VA in STEMI. (B) Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure, AV block, or severe bradycardia. **(C)** Flowchart for the management of electrical storm. **(D)** If similar PVC triggers recurrent polymorphic VA. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-20: ESC Recommendations for management of VA after ACS:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Treatment of VAs in ACS: | | |
| <i>I.V. beta-blocker treatment is indicated for patients with recurrent PVT/VF during STEMI unless contraindicated.</i> | I | B |
| <i>I.V. amiodarone treatment should be considered for patients with recurrent PVT/VF during the acute phase of ACS.</i> | IIa | C |
| <i>I.V. lidocaine may be considered for the treatment of recurrent PVT/VF not responding to beta-blockers or amiodarone, or if amiodarone is contraindicated during the acute phase of ACS.</i> | IIb | C |
| <i>Prophylactic treatment with AADs (other than beta-blockers) is not recommended in ACS.</i> | III | B |
| Treatment of VAs in coronary Vasospasm: | | |
| <i>In SCA survivors with coronary artery spasm, implantation of an ICD should be considered.</i> | IIa | C |
| Risk stratification early after AMI: | | |
| <i>Early (before discharge) assessment of LVEF is recommended in all patients with acute MI.</i> | I | B |
| <i>In patients with pre-discharge LVEF \leq 40%, re-evaluation of LVEF 6-12 weeks after MI is recommended to assess the potential need for primary prevention ICD implantation.</i> | I | C |
| Treatment of VAs early after AMI: | | |
| <i>Catheter ablation should be considered in patients with recurrent episodes of PVT/VF triggered by a similar PVC non-responsive to medical treatment or coronary revascularization in the subacute phase of MI.</i> | IIa | C |

- **Chronic coronary artery disease:**

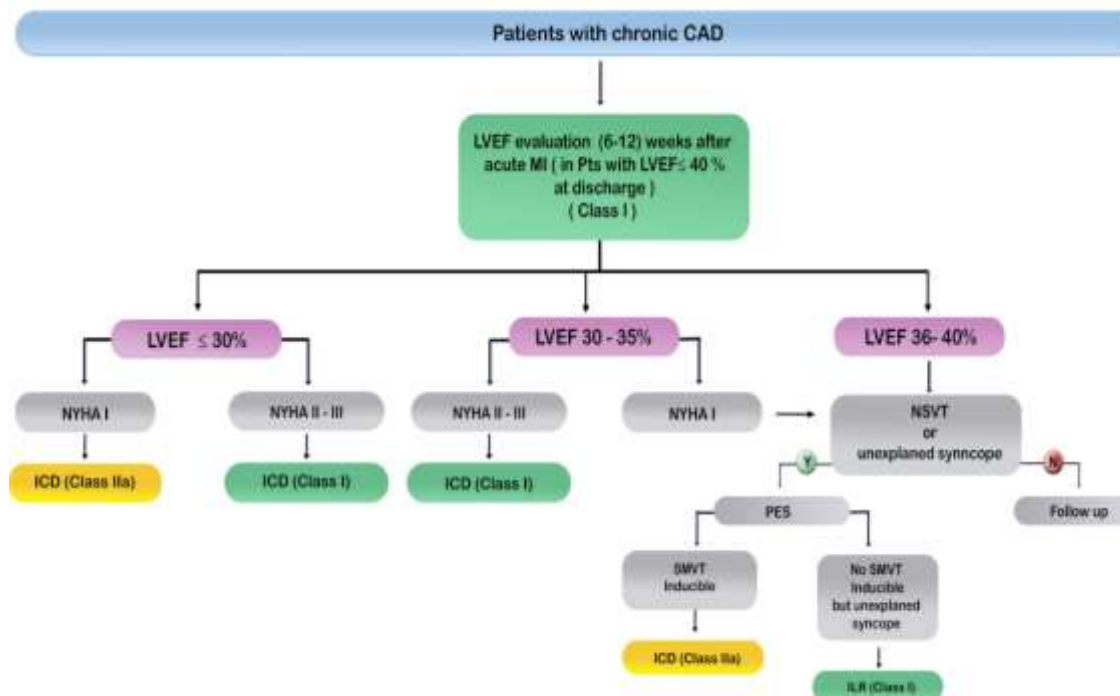


Figure 17-21: Algorithm for risk stratification and primary prevention of SCD in patients with chronic CAD and reduced LVEF. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

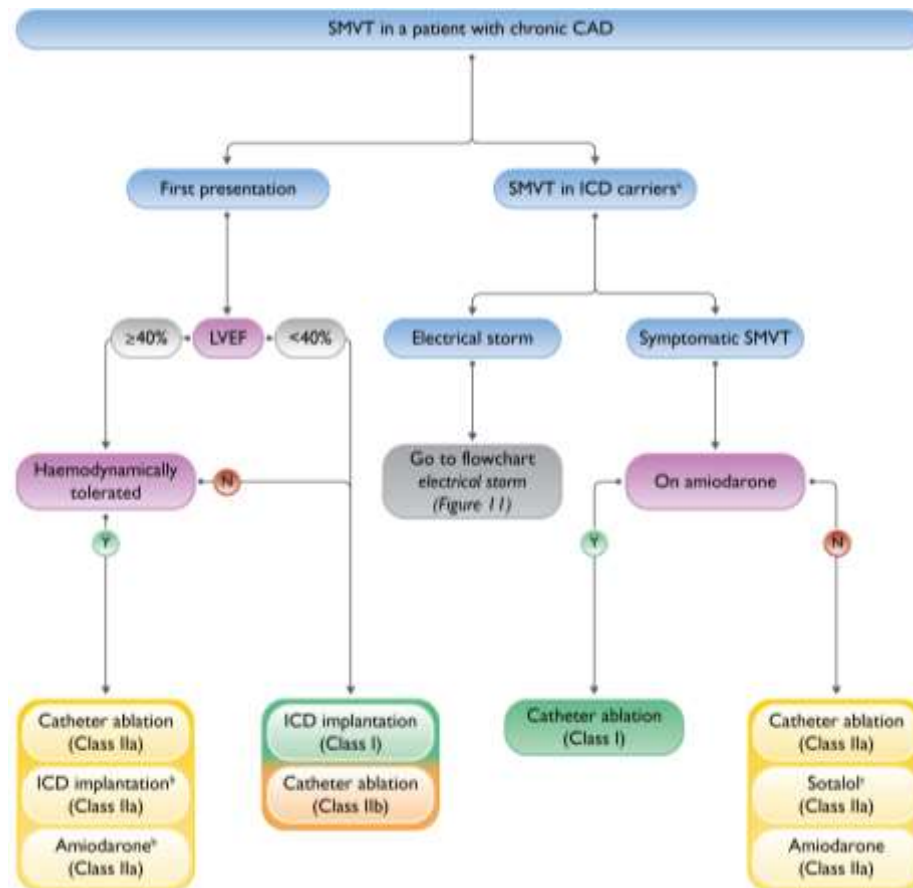


Figure 17-22: Algorithm for the management of sustained monomorphic ventricular tachycardia in patients with chronic coronary artery disease. (A) Incessant ventricular tachycardia in monitor zone: consider catheter ablation. **(B)** If catheter ablation is not available, not successful or not desired by the patient. **(C)** To reduce ICD shocks. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

| Table 17-21: ESC Recommendations for management of ventricular arrhythmias in chronic CAD: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Risk stratification and primary prevention of SCD: | | |
| <i>In patients with syncope and previous STEMI, PES is indicated when syncope remains unexplained after non-invasive evaluation.</i> | I | C |
| <i>ICD therapy is recommended in patients with CAD, symptomatic heart failure (NYHA class II–III), and LVEF $\leq 35\%$ despite ≥ 3 months of OMT.</i> | I | A |
| <i>ICD therapy should be considered in patients with CAD, NYHA class I, and LVEF $\leq 30\%$ despite ≥ 3 months of OMT.</i> | IIa | B |
| <i>ICD implantation should be considered in patients with CAD, LVEF $\leq 40\%$ despite ≥ 3 months of OMT, and NSVT, if they are inducible for SMVT by PES.</i> | IIa | B |
| <i>In patients with CAD, prophylactic treatment with AADs (other than beta-blockers) is not recommended.</i> | III | A |
| Secondary prevention of SCD and treatment of VAs: | | |
| <i>ICD implantation is recommended in patients without ongoing ischemia with documented VF or hemodynamically not-tolerated VT occurring later than 48 h after MI.</i> | I | A |
| <i>In patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite chronic amiodarone therapy, catheter ablation is recommended in preference to escalating AAD therapy.</i> | I | B |
| <i>The addition of oral amiodarone or beta-blocker replacement by sotalol should be considered in patients with CAD with recurrent, symptomatic SMVT, or ICD shocks for SMVT while on beta-blocker treatment.</i> | IIa | B |

| | | |
|---|------------|----------|
| <i>In patients with CAD and hemodynamically well-tolerated SMVT and LVEF \geq 40%, catheter ablation in experienced centres should be considered as an alternative to ICD therapy, provided that established endpoints have been reached ⁽¹⁾.</i> | IIa | C |
| <i>ICD implantation should be considered in patients with a hemodynamically tolerated SMVT and an LVEF \geq40% if VT ablation fails, is not available, or is not desired.</i> | IIa | C |
| <i>Catheter ablation should be considered in patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite beta-blockers or sotalol treatment.</i> | IIa | C |
| <i>In patients with CAD eligible for ICD implantation, catheter ablation may be considered just before (or immediately after) ICD implantation to decrease subsequent VT burden and ICD shocks.</i> | IIb | B |

▪ **Coronary anomalies:**

| Table 17-22: ESC Recommendations for sudden cardiac death prevention in coronary anomalies: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Diagnostic evaluation: | | |
| <i>Cardiac stress imaging during physical exercise is recommended in addition to cardiopulmonary exercise test in patients with anomalous aortic origin of a coronary artery:</i> - with an interarterial course to confirm/exclude myocardial ischemia. - with a history of aborted CA. | I | C |
| Treatment: | | |
| <i>Surgery is recommended in patients with anomalous aortic origin of a coronary artery with CA, syncope suspected to be due to VAs, or angina when other causes have been excluded.</i> | I | C |

(1) VT non-inducibility and elimination of electrograms consistent with conduction delay.

Surgery should be considered in asymptomatic patients with:

- *anomalous aortic origin of a coronary artery and evidence of myocardial ischemia or*
- *abnormal aortic origin of the left coronary artery with high-risk anatomy ⁽¹⁾.*

Ila

C

IV. Cardiomyopathies

See chapter 4: for more details about management of VA prevention of SCD in different cardiomyopathies.

V. Neuromuscular disorders

- Arrhythmias are common and often the first manifestation of neuromuscular disorders.
- Myotonic dystrophy is the most common muscular dystrophy in the adult population (prevalence 1 in 8000). Myotonic dystrophy is the consequence of trinucleotide repeat expansion in the end of **DMPK gene**, which results in mis-splicing of SCN5A and cardiac conduction system delays and arrhythmia.
- Duchenne dystrophy also has a high incidence (1 in 3500 male births). As most patients die before the age of 20, it is rarely seen in adulthood.

(1) *High-risk anatomy is defined as interarterial course, slit-like shaped orifice, high orifice, acute-angle take-off, and intramural course and its length.*

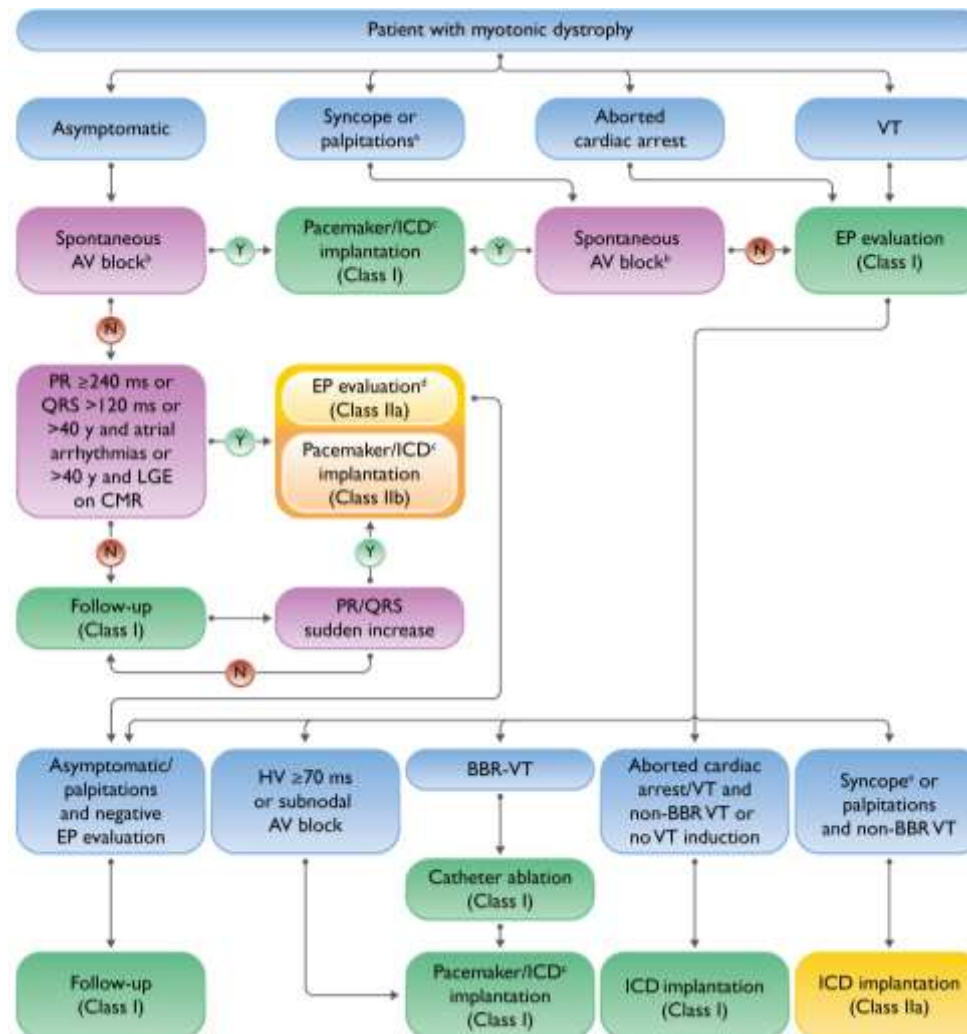


Figure 17-23: Algorithm for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmia in myotonic dystrophy. (A) Syncope or palpitations highly suspicious of arrhythmic origin. (B) Spontaneous AV block: third or advanced second-degree AV block. (C) Factors favouring ICD implantation: age, CTG expansion, sudden death (SD) or family history of SD, ECG conduction abnormalities, PR prolongation, left bundle branch block, atrial arrhythmias, non-sustained VT, LV dysfunction, significant LGE in CMR. (D) Further management according to outcome of EP evaluation. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Table 17-23: ESC Recommendations for management of VA and SCD in neuromuscular diseases:

| Recommendations | Class | Level |
|---|--------------|--------------|
| General recommendations: | | |
| <i>Annual follow-up with at least a 12-lead ECG is recommended in patients with muscular dystrophies, even in the concealed phase of the disease.</i> | I | C |
| <i>It is recommended that patients with neuromuscular disorders who have VAs or ventricular dysfunction are treated in the same way for arrhythmia as patients without neuromuscular disorders.</i> | I | C |
| Risk stratification, primary and secondary prevention of SCD: | | |
| <i>Invasive electrophysiological evaluation is recommended in patients with myotonic dystrophy and palpitations or syncope suggestive of VA or surviving a CA.</i> | I | C |
| <i>Invasive electrophysiological evaluation should be considered in patients with myotonic dystrophy and a PR interval ≥ 240 ms or QRS duration ≥ 120 ms or sudden increase in the PR interval or QRS duration or who are older than 40 years and have supraventricular arrhythmias or who are older than 40 years and have significant LGE on CMR.</i> | IIa | B |
| <i>ICD implantation is recommended in patients with myotonic dystrophy and SMVT or aborted CA not caused by BBR-VT.</i> | I | C |
| <i>In myotonic dystrophy patients, ICD implantation should be considered in:</i> <ul style="list-style-type: none"> - Patients without AV conduction delay and a syncope highly suspicious for VA. - Patients with palpitations highly suspicious for VA and induction of a non-BBR-VT - Patients with limb-girdle type 1B or Emery-Dreifuss muscular dystrophies and indication for pacing | IIa | C |
| <i>Implantation of an ICD may be considered in patients with Duchenne/Becker muscular dystrophy and significant LGE at CMR.</i> | IIb | C |

| | | |
|---|------------|----------|
| <i>Implantation of an ICD over a permanent pacemaker may be considered in myotonic dystrophy patients with additional risk factors ⁽¹⁾ for VAs and SCD.</i> | IIb | C |
| <i>In myotonic dystrophy patients, serial electrophysiological evaluation of AV conduction and arrhythmia induction is not recommended without arrhythmia suspicion or progression of ECG conduction disorders.</i> | III | C |
| Management of VA: | | |
| <i>In symptomatic patients with BBR-VT, catheter ablation is recommended ⁽²⁾.</i> | I | C |
| <i>In patients with myotonic dystrophy undergoing ablation for BBR-VT, pacemaker/ICD implantation is recommended.</i> | I | C |

VI. Inflammatory cardiac diseases

See chapter 4: for more details about management of VA prevention of SCD in different inflammatory cardiac diseases.

VII. Valvular heart disease

- **In patients after TAVI**, SCD has been associated with the presence of new-onset conduction disturbances (LBBB, QRS > 160 ms) and reduced LVEF ≤ 40%.
- **In Mitral Valve Prolapse**, SCD has been reported to occur in 0.2-0.4% of patients with MVP per year. However, the total number of patients dying suddenly with this condition is most likely underestimated.

Proposed criteria for an 'arrhythmic MVP syndrome' that have been associated with an increased risk for SCD include: young adults (most often women), QTc prolongation and/or negative T-wave in inferior ECG leads, Reduced LVEF, mitral annular

(1) Factors favouring ICD implantation: Age, CTG expansion, SD or family history of SD, ECG conduction abnormalities, PR prolongation, LBBB, atrial arrhythmias, non-sustained VT, LV dysfunction, structural abnormalities in CMR.

(2) In other cardiac conditions (e.g. aortic valve replacement) with BBR-VT, catheter ablation is also recommended.

disjunction, bi-leaflet involvement on echocardiography, frequent PVCs, or non-sustained PVT on Holter monitoring and myocardial fibrosis on CMR.

Table 17-24: ESC Recommendations for management of VA and SCD in valvular heart disease:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>PES with standby catheter ablation is recommended in patients with aortic valve disease and SMVT to identify and ablate BBR-VT, especially if it occurs following a valve intervention.</i> | I | C |
| <i>In patients with valvular heart disease and persistent LV dysfunction after surgical correction, (if possible) it is recommended that ICD implantation for primary prevention follows DCM/HNDCM recommendations.</i> | I | C |

VIII. Congenital heart disease

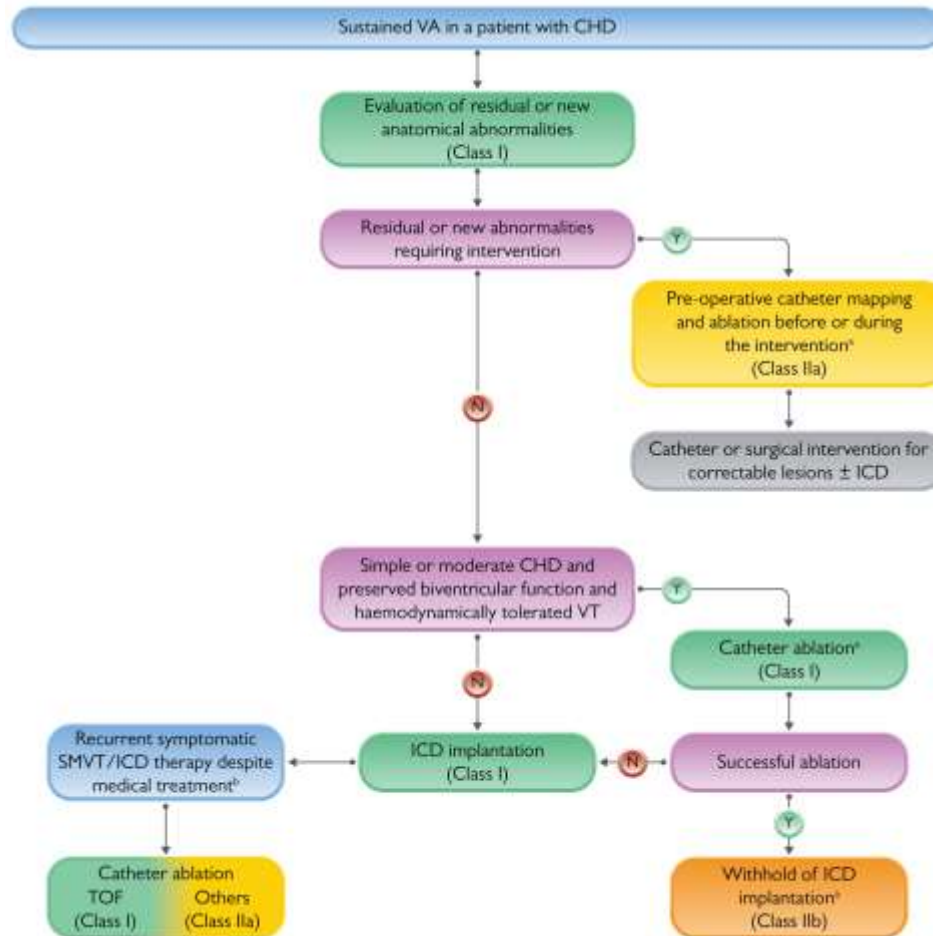


Figure 17-24: Algorithm for the management of sustained ventricular arrhythmia in patients with congenital heart disease. (A) Data derived from patients with TOF and related lesions. **(B)** In TOF, anti-arrhythmic drug failure is not required. **Source:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

| Table 17-25: ESC Recommendations for primary prevention of SCD in congenital heart disease: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| All CHD patients: | | |
| <i>In adults with CHD with biventricular physiology and a left systemic ventricle presenting with symptomatic heart failure (NYHA II/III) and EF ≤ 35% despite ≥ 3 months of OMT, ICD implantation is indicated.</i> | I | C |
| <i>In patients with CHD with presumed arrhythmic syncope and with either at least moderate ventricular dysfunction or inducible SMVT on PES, ICD implantation should be considered.</i> | IIa | C |
| <i>In patients with advanced single ventricle or systemic RV dysfunction with additional risk factors ⁽¹⁾, ICD implantation may be considered.</i> | IIb | C |
| Tetralogy of Fallot: | | |
| <i>In patients after repair of TOF with arrhythmia symptoms and NSVT, electrophysiologic evaluation including PES should be considered.</i> | IIa | C |
| <i>In patients after repair of TOF with arrhythmia symptoms and positive PES, or a combination of other risk factors ⁽²⁾ and positive PES, ICD implantation should be considered.</i> | IIa | C |
| <i>In patients after repair of TOF without arrhythmia symptoms, but with a combination of other risk factors, electrophysiologic evaluation, including PES, may be considered.</i> | IIb | C |

(1) Data are sparse and risk factors may be lesion-specific, including non-sustained VT, NYHA II/III, severe AV valve regurgitation, and wide QRS ≥140 ms (transposition of the great arteries).

(2) Other risk factors include moderate RV or LV dysfunction, extensive RV scarring on CMR, QRS duration ≥ 180 ms and severe QRS fragmentation.

In patients with repaired TOF undergoing surgical or transcatheter pulmonary valve replacement, pre-operative catheter mapping and transection of VT-related anatomical isthmuses before or during the intervention may be considered.

| | |
|------------|----------|
| IIb | C |
|------------|----------|

Table 17-26: ESC Recommendations for secondary prevention of SCD and treatment of VA in congenital heart disease

| Recommendations | Class | Level |
|---|--------------|--------------|
| All CHD patients: | | |
| <i>In patients with CHD presenting with sustained VAs, evaluation for residual lesions or new structural abnormalities is recommended.</i> | I | B |
| <i>In patients with CHD with not tolerated VT/aborted CA due to VF, ICD implantation is indicated after exclusion of reversible causes.</i> | I | C |
| <i>In patients with CHD and recurrent, symptomatic SMVT or ICD shocks for SMVT not manageable by medical therapy or ICD reprogramming, catheter ablation performed in specialized centres should be considered.</i> | IIa | C |
| <i>In selected patients with CHD (including atrial baffle repair for transposition of the great arteries, Fontan operation and Ebstein anomaly) presenting with CA, evaluation and treatment of SVT with rapid ventricular conduction should be considered.</i> | IIa | C |
| Tetralogy of Fallot: | | |
| <i>In patients with repaired TOF who present with SMVT or recurrent, symptomatic appropriate ICD therapy for SMVT, catheter ablation performed in specialized centres is recommended.</i> | I | C |

| | | |
|---|------------|----------|
| <i>In patients with repaired TOF with SMVT who are undergoing surgical or transcutaneous pulmonary valve replacement, pre-operative catheter mapping and transection of VT-related anatomical isthmuses before or during the intervention should be considered.</i> | IIa | C |
| <i>In patients with repaired TOF with a preserved biventricular function and symptomatic SMVT, catheter ablation or concomitant surgical ablation performed in specialized centres may be considered as an alternative to ICD therapy.</i> | IIb | C |

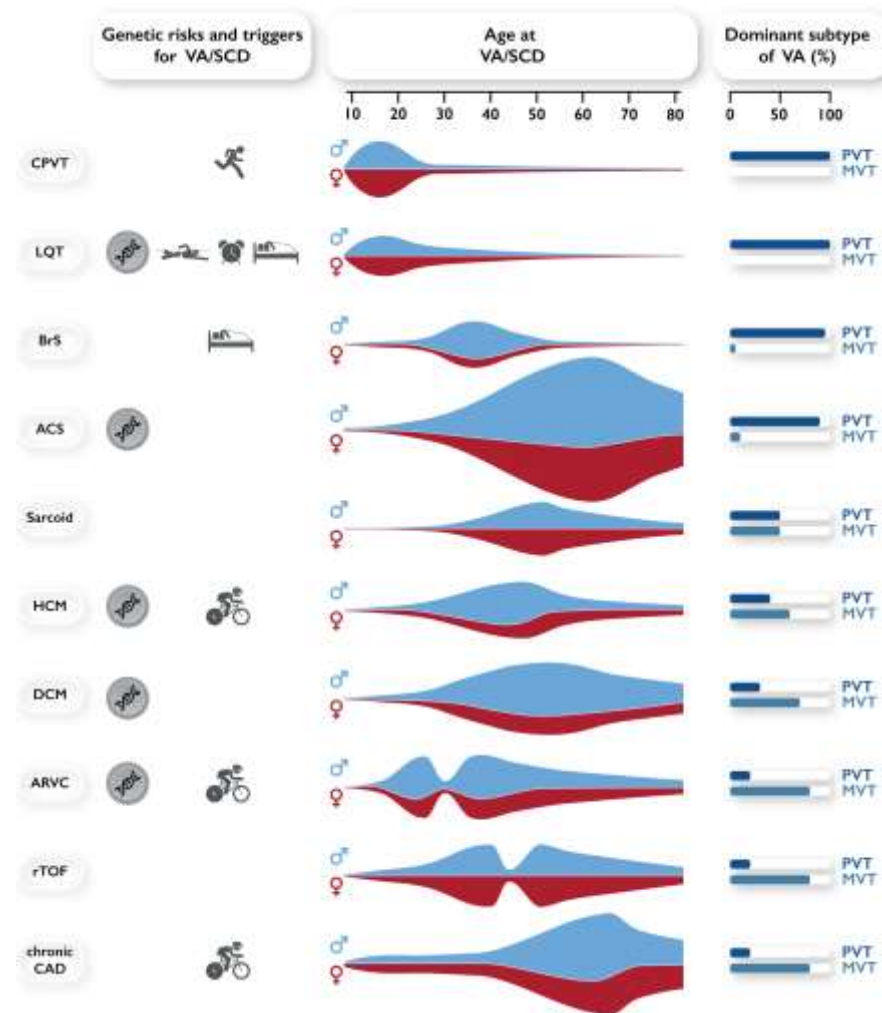


Figure 17-25: Genetic risk for VA/SCD, typical triggers for VA/SCD, age at presentation with VA/SCD, sex predominance, and typical VA (PVT/VF vs. MVT) in different diseases associated with VA/SCD. Source: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

Special aspects in selected populations:

▪ Pregnant patients and peri-partum cardiomyopathy:

New-onset VT may present during pregnancy and risk of recurrent VT is higher in patients with previous VT and SHD. Peri-partum cardiomyopathy (PPCM) should be ruled out in the case of new-onset VT during the last 6 weeks of pregnancy or in the early post-partum period. A genetic contribution may be present in up to 20% of patients with PPCM (in particular titin-truncating variants).

Table 17-27: ESC recommendations for the prevention of sudden cardiac death and management of ventricular arrhythmia during pregnancy:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Acute management of VA: | | |
| <i>During pregnancy, electrical cardioversion is recommended for sustained VT.</i> | I | C |
| <i>For acute conversion of hemodynamically tolerated SMVT during pregnancy, a beta-blocker, sotalol, flecainide, procainamide, or overdrive ventricular pacing should be considered.</i> | IIa | C |
| Long-term management of VA: | | |
| <i>If ICD implantation is indicated during pregnancy, implantation is recommended with optimal radiation protection.</i> | I | C |
| <i>Continuation of beta-blockers during pregnancy and post-partum is recommended in women with LQTS or CPVT.</i> | I | C |
| <i>Continuation of beta-blockers during pregnancy should be considered in women with ARVC.</i> | IIa | C |
| <i>Oral metoprolol, propranolol, or verapamil should be considered for long-term management of idiopathic sustained VT during pregnancy.</i> | IIa | C |

Catheter ablation using non-fluoroscopic mapping systems should be considered, preferably after the first trimester, in women with highly symptomatic recurrent SMVT refractory or who are intolerant to AADs.

IIa

C

▪ **Heart transplantation:**

Table 17-28: ESC recommendations for the prevention of sudden cardiac death before and after heart transplantation:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Prior to heart transplant: | | |
| <i>In patients awaiting heart transplantation, ICD implantation for primary prevention should be considered.</i> | IIa | C |
| <i>In patients awaiting heart transplantation, WCD may be considered.</i> | IIb | C |
| Post heart transplant: | | |
| <i>In selected transplanted patients with cardiac allograft vasculopathy or treated rejection, ICD implantation may be considered.</i> | IIb | C |

▪ **Sudden cardiac death in athletes:**

In apparently healthy athletes (> 35 years), the estimated incidence of SCD ranges from 2 to 6.3 per 100 000 participant-years. In comparison, in young competitive athletes (\leq 35 years) the incidence of fatal events is significantly lower, 0.4-3 per 100 000 participant years.

Table 17-29: ESC recommendations for risk stratification and prevention of SCD in athletes:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|--|------------|----------|
| <i>In athletes with positive medical history, abnormal physical examination, or ECG alterations, further investigations including echocardiography and/or CMR to confirm (or exclude) an underlying disease are recommended.</i> | I | C |
| <i>It is recommended that athletes diagnosed with a cardiovascular disease associated with SCD are managed according to current guidelines for sports eligibility.</i> | I | C |
| <i>It is recommended that staff at sporting facilities is trained in CPR and in the use of AED.</i> | I | C |
| <i>Pre-participation cardiovascular evaluation of competitive athletes should be considered.</i> | IIa | C |
| <i>It should be considered that cardiovascular evaluation of young (< 35 years) competitive athletes includes history, physical examination, and 12-lead ECG.</i> | IIa | C |
| <i>The cardiovascular risk of middle-aged and elderly individuals should be evaluated before engaging in strenuous sports through established scores such as the SCORE2 risk chart.</i> | IIa | C |

Important trials in Ventricular Arrhythmias:

Table 17-30: Clinical trials in Ventricular arrhythmias:

| Trial (date) | Summary |
|----------------------------------|---|
| Ventricular Fibrillation: | |
| ARREST (1999) | <p>Aim: To assess if I.V amiodarone improve resuscitation during cardiac arrest as measured by survival to admission to the hospital.</p> <p>Study: 504 patients who had cardiac arrest with ventricular fibrillation (or pulseless ventricular tachycardia) and who had not been resuscitated after receiving three or more precordial shocks were randomly assigned to receive intravenous amiodarone (300 mg) or placebo. Amiodarone resulted in a higher rate of survival to hospital admission. Whether this benefit extends to survival to discharge from the hospital merits further investigation.</p> |
| ALIVE (2002) | <p>Aim: To compare the safety and efficacy of I.V amiodarone with lidocaine for the prehospital treatment of shock-refractory VF.</p> <p>Study: 344 patients with out-of-hospital VF resistant to three shocks, I.V epinephrine, and a further shock; or if they had recurrent VF after initially successful defibrillation were randomly assigned to receive intravenous amiodarone plus lidocaine placebo or i.v lidocaine plus amiodarone placebo. Amiodarone leads to substantially higher rates of survival to hospital admission in patients with shock-resistant out-of-hospital VF.</p> |
| Ventricular Tachycardia: | |
| VANISH (2016) | <p>Aim: To evaluate VT ablation versus escalation of antiarrhythmic drug therapy among individuals with an ischemic cardiomyopathy and ICD who had VT despite antiarrhythmic drug therapy.</p> <p>Study: 259 patients with ischemic cardiomyopathy and an ICD who had VT despite antiarrhythmic drug therapy, were randomly assigned to receive either catheter ablation (ablation group) with continuation of baseline antiarrhythmic medications or escalated antiarrhythmic drug therapy (escalated-therapy group). In the escalated-therapy group,</p> |

| | |
|--------------------------|--|
| | <i>amiodarone was initiated if another agent had been used previously. There was a significantly lower rate of the composite primary outcome of death, ventricular tachycardia storm, or appropriate ICD shock among patients undergoing catheter ablation than among those receiving an escalation in antiarrhythmic drug therapy.</i> |
| PROCAMIO (2017) | <p>Aim: <i>To determine the safety and efficacy of i.v procainamide and amiodarone for the acute treatment of tolerated wide QRS complex (probably ventricular) tachycardia.</i></p> <p>Study: <i>74 patients with acute episode of sustained monomorphic well-tolerated VT were randomly assigned to receive intravenous procainamide (10 mg/kg/20 min) or amiodarone (5 mg/kg/20 min). The primary endpoint was the incidence of major predefined cardiac adverse events within 40 min after infusion initiation. Procainamide therapy was associated with less major cardiac adverse events and a higher proportion of tachycardia termination within 40 min.</i></p> |
| VTACH (2010) | <p>Aim: <i>To assess the potential benefit of catheter ablation before implantation of an ICD.</i></p> <p>Study: <i>110 patients aged 18-80 years with stable VT, previous MI, and reduced LVEF (EF ≤ 50%) were randomly assigned to receive catheter ablation and an ICD (ablation group) or ICD alone (control group). Prophylactic VT ablation before ICD seemed to prolong time to recurrence of VT in patients with stable VT, previous MI, and reduced LVEF. Prophylactic catheter ablation should be considered before implantation of an ICD in such patients.</i></p> |
| EARLY-BAMI (2016) | <p>Aim: <i>To assess the safety and efficacy of early administration of i.v metoprolol in patients presenting with STEMI and scheduled for primary PCI.</i></p> <p>Study: <i>683 STEMI patients presenting < 12 h from symptom onset in Killip class I to II without AV block were randomized to IV metoprolol (2 × 5-mg bolus) or matched placebo before PPCI. Primary endpoint was myocardial infarct size as assessed by cardiac MRI at 30 days. Early intravenous metoprolol before PPCI was not associated with a reduction in infarct size. Metoprolol reduced the incidence of malignant arrhythmias in the acute phase and was not associated with an increase in adverse events.</i></p> |

References and suggested readings:

- Zeppenfeld K, Tfelt-Hansen J, De Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). *European heart journal*. 2022 Oct 21;43(40):3997-4126.
- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).
- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier
- Olshansky, Brian, et al. *Arrhythmia Essentials*. Elsevier, 2017.
- <https://litfl.com/ecg-library/>

Chapter 18:

Bradyarrhythmias

Classification:

Table 18-1: Definitions of sinus, atrioventricular junction, and intraventricular conduction disturbances:

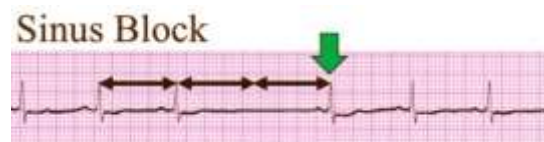
Sinus Node Disorders:

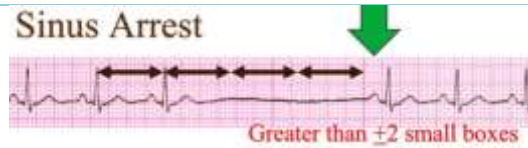
1. **Sinus bradycardia:** sinus rate < 60 b.p.m.



2. **Sinus pause:** absence of sinus P waves for ≥ 2 s (sinus pause ≥ 3 s is very uncommon in physiological settings). Sinus pause may be a consequence of sinus arrest or SA exit block. In sinus arrest, electrical impulses are not properly generated whereas in sinus block, although there is no problem with the production of electrical signals, the signals are not properly transmitted into the myocardial cells.

On ECG, The duration of the pause with Sinus Exit Block is in a direct multiple of the R to R interval of the underlying rhythm (+/- 2 small boxes). Sinus Arrest does not have this specific feature.





3. **Bradycardia-tachycardia syndrome:** bradycardia alternating with paroxysmal supraventricular arrhythmias, most frequently atrial fibrillation. The tachycardia may be associated with suppression of sinus node automaticity and a sinus pause of variable duration when the tachycardia terminates.



4. **Sinus arrhythmia:** phasic changes in P–P interval, often related to respiration. The sinus rate gradually increases with inspiration as the left output decreases; thus, P–P interval gets shorter with inspiration. The difference between the smallest and the longest P–P intervals is > 120 ms or $> 10\%$ of the smallest interval.



5. **Chronotropic incompetence:** inability to increase the heart rate to 85% of the maximal predicted heart rate (MPHR) during exercise, or 80% of the expected heart rate reserve ⁽¹⁾.

Sick sinus syndrome is any of the preceding disorders (1–5) due to an intrinsic sinus node disease, often degenerative in nature. Tachy– brady syndrome occurs in 55–75% of cases of sick sinus syndrome.

AV junction disorders:

1. **First degree:** PR > 200 ms associated with 1:1 AV conduction.

(1) *Maximal predicted heart rate* = $220 - \text{Age}$.

Expected heart rate reserve = *Maximal predicted heart rate* - *Resting heart rate* ($220 - \text{Age} - \text{Resting heart rate}$).



2. **Second degree:** P waves with a constant rate (< 100 b.p.m.) where AV conduction is present but not 1:1.
- **Mobitz type I or Wenckebach:** PR interval progressively prolongs until QRS drops, i.e., until a regularly occurring P wave is not followed by a QRS. To make the diagnosis, compare the PR that follows the blocked P wave (the shortest PR) with the PR that immediately precedes the blocked P wave (the longest PR).
 - **Mobitz type II:** QRS suddenly drops without a preceding PR change. The baseline QRS is usually wide. It is more ominous than Mobitz type I and is almost always a distal infranodal AV block. It progresses to a complete infranodal AV block commonly and suddenly.
 - **2:1 AV block:** P waves with a constant rate (or near-constant rate because of ventriculophasic sinus arrhythmia) where every second beat is non-conducted ⁽¹⁾.
 - **Advanced or high-grade AV block (e.g 3:1 AVB):** means only one of 3 consecutive P waves is conducted (three P waves with one QRS).

(1) Look carefully for 2:1 AV block in any case of sinus bradycardia. 2:1 AV block may mimic sinus bradycardia when the blocked P waves fall on the preceding T waves and go unnoticed or get mistaken for U waves. Conversely, in patients with sinus bradycardia, U waves may be misinterpreted as blocked P waves, causing a false diagnosis of AV block. Blocked P waves are distinguished from U waves by the fact that they march out almost equidistantly with the P waves that precede the QRS complexes, whereas U waves do not. Also, P waves are often more peaked than U waves.



3. **Third degree:** no evidence of AV conduction ⁽¹⁾. The escape is ventricular with a wide QRS complex if the block is infranodal (rate 20–40 bpm). The escape is junctional with a narrow QRS complex if the block is at the nodal level (rate 40–60 bpm); the junctional escape may be wide if a bundle branch block is present on the baseline ECG. Patients with complete AV block at the infranodal level may have preserved VA conduction, and retrograde P waves may be seen.



Intraventricular conduction disturbance:

The His bundle branches into the right bundle and left bundle, which branches into the left anterior fascicle and the left posterior fascicle.

RBBB

(1) AV dissociation is present in all cases of complete AV block, but AV dissociation does not imply AV block.

A competing accelerated junctional or ventricular rhythm that is equal in rate to the sinus rhythm, or faster than it, may lead to AV dissociation. One form of competing AV dissociation is isorhythmic AV dissociation, in which the junctional or ventricular rhythm almost has the same rate as the sinus rhythm, allowing intermittent conduction of sinus P waves that are falling far enough from the QRS complexes (e.g., AIVR, accelerated junctional rhythm). One beat may be a sinus beat preceded by a P wave, the other may be a junctional beat dissociated from P wave and showing up at any deceleration of the sinus rate. AV block is implied when a P wave falls far enough from the QRS complex yet does not get conducted.

- **Advanced RBBB** ⁽¹⁾: QRS ≥ 120 ms with variable QRS axis (extreme right or left-axis deviation may be seen when there is also an inferoposterior or superoanterior fascicular block). ECG features include:
 - rsR' in V1 and V2 with slurring in R' wave; slightly depressed ST in V1 and an asymmetrical negative T wave in V1-V2 and occasionally in V3.
 - qRs in I, aVL and V4-V6 with slurring in 's' wave.
 - QR in aVR with slurring in R, and negative T wave
- **Partial RBBB**: QRS width < 120 ms. ECG features include:
 - rSr' in V1. The r' is not wide and may have a variable voltage.
 - terminal, not wide, 'r' in aVR, and 's' in I and V6.



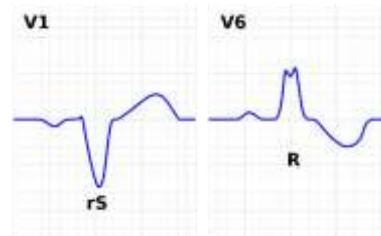
LBBB:

- **Advanced LBBB**: QRS ≥ 120 ms. ECG features include:
 - QS or rS in V1 with small 'r' with ST slightly elevated and positive asymmetrical T wave.
 - Unique R wave in V6 with negative asymmetric T wave. When the QRS is < 140 ms, the T wave in V6 may be positive.
 - Exclusive R wave in I and aVL often with a negative asymmetrical T wave, slight ST depression, and
 - Usually, QS in aVR with positive T wave.
 - Generally, the ST segment is slightly opposed to the QRS polarity.

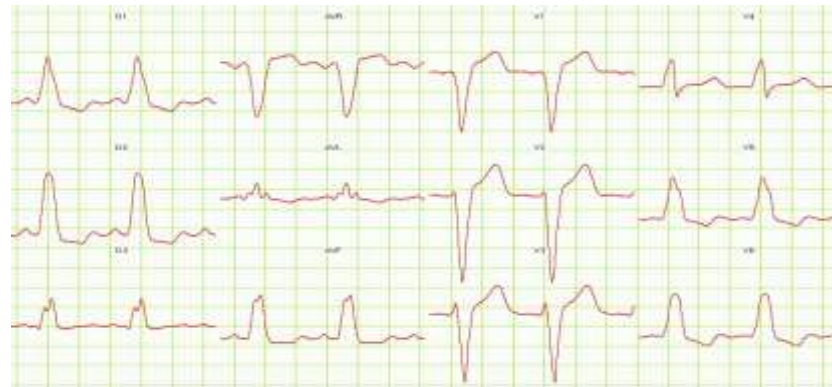
(1) The terms 'advanced' and 'not complete bundle branch block' are used, because it is difficult to know if the conduction of the stimulus through the affected branch would still be possible, very slowly, if the transseptal depolarization from the other ventricle does not exist or is even slower. In accordance, the term partial block is used instead of incomplete block.

○ **Partial LBBB:** QRS < 120 ms. ECG features include:

- Single R in I, aVL, and V6. Repolarization in V6 may be positive or flat/negative according to the accompanying pathology and degree of transseptal depolarization.



Non-specific intraventricular conduction delay (in adults): QRS duration > 110 ms where morphology criteria for RBBB or LBBB are not present.



Left anterior fascicular block (Superoanterior hemiblock) ⁽¹⁾:

- Leftwards QRS axis between -45 and -75.
- qR in I and aVL; rS in II, III, and aVF, with S3 greater than S2, R2 greater than 3, and sometimes terminal r in aVR.
- S until V6 with IDT in V6 less than IDT in aVL, and with IDT in aVL \geq 50 ms.

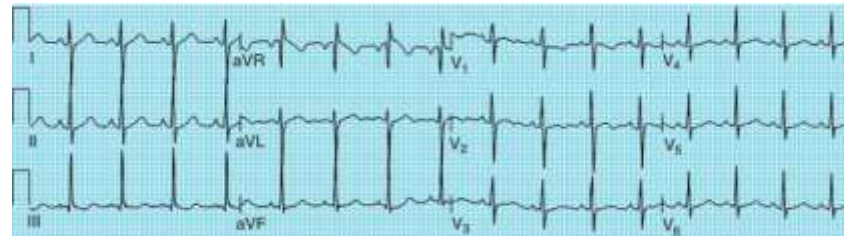
(1) Left septal fascicular block was also suggested [criteria: prominent R wave in V1-V2 and lack of septal q (lack of q in leads V5 and I)]; however, these criteria have a differential diagnosis and at this point this entity is not universally accepted.

- QRS duration < 120 ms. However, in isolated cases the QRS may not surpass 100 ms.
- In advanced cases, mid-terminal slurring is present in I and aVL.



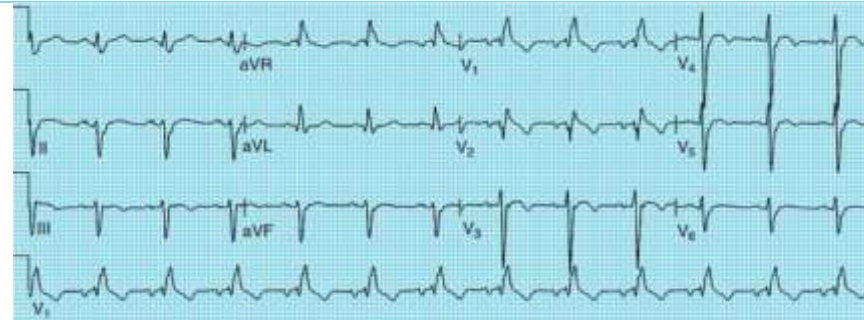
Left posterior fascicular block (Inferoposterior hemiblock):

- QRS axis greatly deviated to the right (between +90 and +140).
- rS in I and aVL, and qR in II, III, and aVF.
- QRS width < 120 ms.
- IDT \geq 50 ms in aVF and V6, with IDT < 50 ms in aVL.
- Mid-terminal slurring in II, III, and aVF in advanced cases (in the absence of partial RBBB).

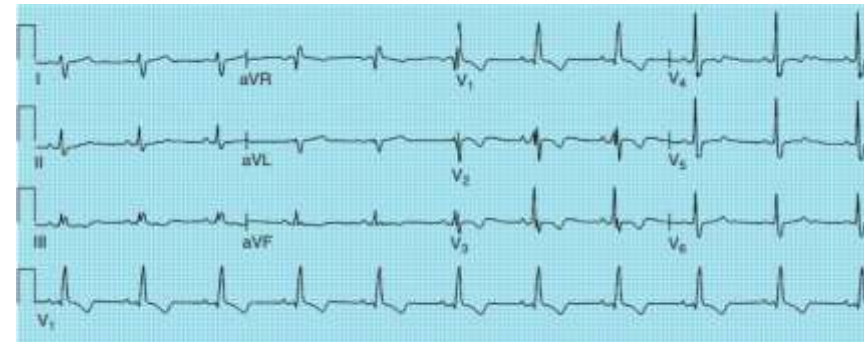


Bifascicular block implies a block in two of the three conduction fascicles, such as:

- LBBB
- or RBBB + LAFB (~ RBBB with left axis)
- or RBBB + LPFB (~ RBBB with right axis, which may also be RBBB + RVH).



RBBB plus LAFB



RBBB plus LPFB

Trifascicular block: all three fascicles have a conduction block. The block is incomplete in at least one fascicle, explaining the lack of complete AV block. Trifascicular block may manifest as:

- Bifascicular block + increased PR interval: this is often a trifascicular block, but may also be a bifascicular block with a first-degree AV block.
- Alternating RBBB and LBBB, i.e., RBBB and LBBB alternate on the same ECG or on different ECGs obtained up to several years apart.
- RBBB with alternating LAFB and LPFB.



N.B:

☞ Causes of a pause on the rhythm strip:

Outside the pause that follows an obvious PAC or PVC, a pause on a rhythm strip may be secondary to:

1. **Sinus pause:** no P wave is seen within the pause.
2. **Second-degree AV block** (Mobitz I or Mobitz II): a blocked P wave is seen within the pause. The blocked P wave marches out with the regularly occurring sinus P wave. Occasionally, however, if sinus arrhythmia is present, the blocked P wave of the AV block may not perfectly march out with the other P waves ⁽¹⁾.
3. **Blocked PAC** (the most benign pause): the blocked P wave is a very premature P wave that falls in the AV nodal refractory period and does not get conducted. As opposed to AV block, the blocked P wave does not march out with the sinus P waves and often has a different morphology.
4. **Concealed premature junctional complex** (less common): a premature junctional complex (His complex) is rare, much less common than a PAC or a PVC. A blocked premature junctional complex prevents the conduction of the next sinus impulse through the His (still in refractory period), creating the impression of a Mobitz II AV block. The presence of conducted premature junctional complexes elsewhere on the rhythm monitor is a hint to this phenomenon.

☞ Location of the AV block:

AV block may occur at the level of the AV node or at the infranodal level, i.e., at the His or the infra-His/Purkinje level.

(1) A particular form of sinus arrhythmia seen with AV block (especially 2:1 AV block) is *ventriculophasic sinus arrhythmia*, in which the P–P interval containing a QRS is shorter than the P–P interval not containing a QRS (the QRS complex leads to a stroke volume which leads to reflex slowing of the P–P interval).

Infranodal AV block is ominous and leads to a slow ventricular escape rhythm. Usually, in infranodal AV block, the baseline QRS is wide as the fascicles have abnormal baseline conduction. Occasionally, the block is at the His level and the baseline QRS may not be wide.

Nodal AV block is less ominous and leads to a faster, junctional, narrow escape rhythm.

Location of the block in each type of AV block:

- **First-degree AV block** is usually a nodal block, particularly if QRS is narrow.
- **Mobitz I** is often a nodal block, especially when QRS is narrow. When the QRS is wide, 75% of Mobitz I blocks are still nodal blocks, while 25% are infranodal blocks.
- **Mobitz II** is an infranodal block, with a QRS that is often wide on the baseline ECG. If the baseline QRS is narrow, the block is likely infranodal at the level of the His bundle (~20% of Mobitz II block).
- **2:1 AV block**: analyze the QRS width and the PR interval to define the site of the block: If QRS is wide, the block is likely infranodal; if QRS is narrow, the block is likely nodal.
- **Third-degree AV block or high-grade AV block** (e.g., 3:1, 4:1) is most often infranodal, but can be nodal. Determine the location of the AV block by the width and the rate of the escape. It is infranodal block if the escape rhythm is wide or if there is VA conduction (retrograde P waves).

Evaluation:

▪ History and Physical examination:

| Table 18-2: Intrinsic and extrinsic causes of bradycardia: | | |
|---|--------------------------|------------------|
| | Sinus bradycardia or SND | AVJ disturbances |
| Intrinsic | | |
| <i>Idiopathic (ageing, degenerative), Infarction/ischaemia, Cardiomyopathies, Genetic disorders</i> | + | + |

| | | |
|--|---|---|
| Infiltrative diseases | | |
| <i>Sarcoidosis, Amyloidosis, Haemochromatosis</i> | + | + |
| Collagen vascular diseases | | |
| <i>Rheumatoid arthritis, Scleroderma, SLE, Storage diseases, neuromuscular diseases</i> | + | + |
| Infectious diseases | | |
| <i>Chagas disease</i> | + | + |
| <i>Endocarditis (perivalvular abscess), Myocarditis, Lyme disease, Diphtheria, Toxoplasmosis</i> | – | + |
| Congenital heart diseases | + | + |
| Cardiac surgery | | |
| <i>CABG, Valve surgery (including TAVR), Radiation therapy, Heart transplant</i> | + | + |
| <i>Maze operation, Sinus tachycardia ablation</i> | + | – |
| <i>Intended or iatrogenic AVB</i> | – | + |
| Extrinsic | | |
| <i>Physical training (sports), Vagal reflex, Drug effects</i> | + | + |
| <i>Idiopathic paroxysmal AVB</i> | – | + |

| | | |
|---|---|---|
| Electrolyte imbalance | | |
| <i>Hypokalaemia, Hyperkalaemia, Hypercalcaemia, Hypermagnesemia</i> | + | + |
| Metabolic disorders | | |
| <i>Hypothyroidism, Anorexia, Hypoxia, Acidosis</i> | + | + |

| Table 18-3: Drugs that may cause bradycardia or conduction disorders: | | |
|--|-------------------------------|-----------------|
| | Sinus node bradycardia | AV bLock |
| <i>Beta-blockers</i> | + | + |
| Antihypertensives | | |
| <i>Non-dihydropyridine CCBs</i> | + | + |
| <i>Methyldopa, Clonidine</i> | + | – |
| Antiarrhythmics | | |
| <i>Amiodarone, Dronedarone, Sotalol, Flecainide, Digoxin, Propafenone, Adenosine, Disopyramide</i> | + | + |
| <i>Procainamide</i> | – | + |
| <i>Ivabradine</i> | + | – |
| Psychoactive and neuroactive drugs | | |
| <i>Donepezil, Lithium, Carbamazepine, Phenothiazine, Phenytoin</i> | + | + |
| <i>Opioid analgesics</i> | + | – |

| | | |
|--|---|---|
| <i>SSRI, Tricyclic antidepressants</i> | – | + |
| Others | | |
| <i>Muscle relaxants, Cannabis, Propofol, High-dose corticosteroids, PPIs</i> | + | – |
| <i>Ticagrelor, H2 antagonists</i> | + | + |
| <i>Chloroquine</i> | – | + |
| Chemotherapy | | |
| <i>Arsenic trioxide, Bortezomib, Cyclophosphamide, 5-fluorouracil, Mitoxantrone, Rituximab, Thalidomide</i> | + | + |
| <i>Capecitabine, Cisplatin, Doxorubicin, Epirubicin, Ifosfamide, Interleukin-2, Methotrexate, Paclitaxel</i> | + | – |
| <i>Anthracycline, Taxane</i> | – | + |

▪ **Diagnostic workup:**

| Table 18-4: Diagnosing bradyarrhythmic syncope after the initial evaluation: | |
|---|---|
| Prolonged ECG monitoring strategy | Provocative (laboratory) test strategy |
| <ul style="list-style-type: none"> • <i>Holter</i> • <i>External loop recorder</i> • <i>Remote at-home telemetry</i> • <i>Implantable loop recorder</i> | <ul style="list-style-type: none"> • <i>Carotid sinus massage</i> • <i>Tilt table test</i> • <i>Electrophysiological study</i> • <i>Exercise test</i> |

| Table 18-5: ESC Recommendations for diagnostic work up of bradyarrhythmia: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Ambulatory ECG monitoring: | | |
| Ambulatory ECG monitoring is recommended in the evaluation of patients with suspected bradycardia to correlate rhythm disturbances with symptoms. | I | C |
| In patients with infrequent (less than once a month) unexplained syncope or other symptoms suspected to be caused by bradycardia, in whom a comprehensive evaluation did not demonstrate a cause, long-term ambulatory monitoring with an ILR is recommended ⁽¹⁾ . | I | A |
| Imaging before implantation: | | |
| Cardiac imaging is recommended in patients with suspected or documented symptomatic bradycardia to evaluate the presence of structural heart disease, to determine LV systolic function, and to diagnose potential causes of conduction disturbances. | I | C |
| Multimodality imaging (CMR, CT, or PET) should be considered for myocardial tissue characterization in the diagnosis of specific pathologies associated with conduction abnormalities needing pacemaker implantation, particularly in patients < 60 years. | IIa | C |
| Laboratory tests: | | |
| In addition to pre-implantation laboratory tests (CBC, PT, PTT, S. creatinine, and electrolytes), specific laboratory tests are recommended in patients with clinical suspicion for potential underlying causes of reversible bradycardia (e.g., thyroid function tests, Lyme titre, digitalis level, potassium, calcium, and pH) to diagnose and treat these conditions. | I | C |
| Carotid sinus massage (CSM): | | |

(1) ILR is an ideal diagnostic tool given its capacity for prolonged monitoring (up to 3 years) and without the need for active patient participation.

| | | |
|---|------------|----------|
| <i>Once carotid stenosis is ruled out ⁽¹⁾, CSM is recommended in patients with syncope of unknown origin compatible with a reflex mechanism or with symptoms related to pressure/manipulation of the carotid sinus area (e.g., tight collars, shaving, or turning the head).</i> | I | B |
| Exercise testing: | | |
| <p>Exercise testing can be used to diagnose symptomatic chronotropic incompetence. However, some medical treatments and comorbidities cause exercise intolerance and make the diagnosis of chronotropic incompetence by exercise testing more difficult.</p> <p>Also, in patients with exercise-related symptoms, the development or progression of AVB may occasionally be the underlying cause. Tachycardia-related exercise-induced second-degree and complete AVB have been shown to be located distal to the AVN and predict progression to permanent AVB.</p> | | |
| <i>Exercise testing is recommended in patients who experience symptoms suspicious of bradycardia during or immediately after exertion.</i> | I | C |
| <i>In patients with suspected chronotropic incompetence, exercise testing should be considered to confirm the diagnosis.</i> | IIa | B |
| <i>In patients with intraventricular conduction disease or AVB of unknown level, exercise testing may be considered to expose infranodal block.</i> | IIb | C |
| Genetic testing: | | |
| Early-onset progressive cardiac conduction disease (PCCD), either isolated or with concomitant structural heart disease, should prompt consideration of genetic testing, particularly in patients with a positive family history of conduction abnormalities, pacemaker implants, or sudden death. | | |

(1) CSM should not be undertaken in patients with previous TIA, stroke, or known carotid stenosis. Carotid auscultation should be performed before CSM. If a carotid bruit is present, carotid ultrasound should be performed to exclude carotid disease.

| | | |
|---|------------|----------|
| <i>Genetic testing should be considered in patients with early onset (age < 50 years) of progressive cardiac conduction disease (Prolonged P wave duration, PR interval and QRS widening with axis deviation).</i> | IIa | C |
| <i>Genetic testing should be considered in family members following the identification of a pathogenic genetic variant that explains the clinical phenotype of cardiac conduction disease in an index case.</i> | IIa | C |
| Sleep Evaluation: | | |
| <p>Nocturnal bradyarrhythmias are common in the general population. In most circumstances, these are physiological, vagally mediated asymptomatic events, which do not require intervention.</p> <p>Patients with sleep apnea syndrome (SAS) have a higher prevalence of sleep-related bradycardia (both sinus and conduction system related) during apnoeic episodes. SAS-induced hypoxemia is a key mechanism leading to an increased vagal tone and bradycardic rhythm disorders. Treatment with CPAP alleviates OSA-related symptoms and improves CV outcomes. Appropriate treatment reduces episodes of bradycardia by 72-89%, and patients are unlikely to develop symptomatic bradycardia at longterm follow-up.</p> | | |
| <i>Screening for SAS is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep.</i> | I | C |
| Tilt testing: | | |
| <p>Tilt testing: should be considered to confirm a diagnosis of reflex syncope in patients in whom this diagnosis was suspected but not confirmed by initial evaluation. The endpoint of tilt testing is the reproduction of symptoms along with the characteristic circulatory pattern of the reflex syncope.</p> <p>A positive cardioinhibitory response to tilt testing predicts, with high probability, asystolic spontaneous syncope; this finding is relevant for therapy when cardiac pacing is considered. Conversely, the presence of a positive vasodepressor, a mixed response, or even a negative response does not exclude asystole during syncope.</p> | | |

| | | |
|---|------------|----------|
| <i>Tilt testing should be considered in patients with suspected recurrent reflex syncope.</i> | IIa | B |
| Electrophysiology study: | | |
| <i>In patients with syncope and bifascicular block, EPS should be considered when syncope remains unexplained after non-invasive evaluation or when an immediate decision about pacing is needed due to severity, unless empirical pacemaker implantation is preferred (especially in elderly and frail patients) ⁽¹⁾.</i> | IIa | B |
| <i>In patients with syncope and sinus bradycardia, EPS may be considered when non-invasive tests have failed to show a correlation between syncope and bradycardia.</i> | IIb | B |

(1) *The efficacy of EPS for the diagnosis of syncope is highest in patients with sinus bradycardia, bifascicular block, and suspected tachycardia, and lowest in patients with normal ECG, no structural heart disease, and no palpitations.*

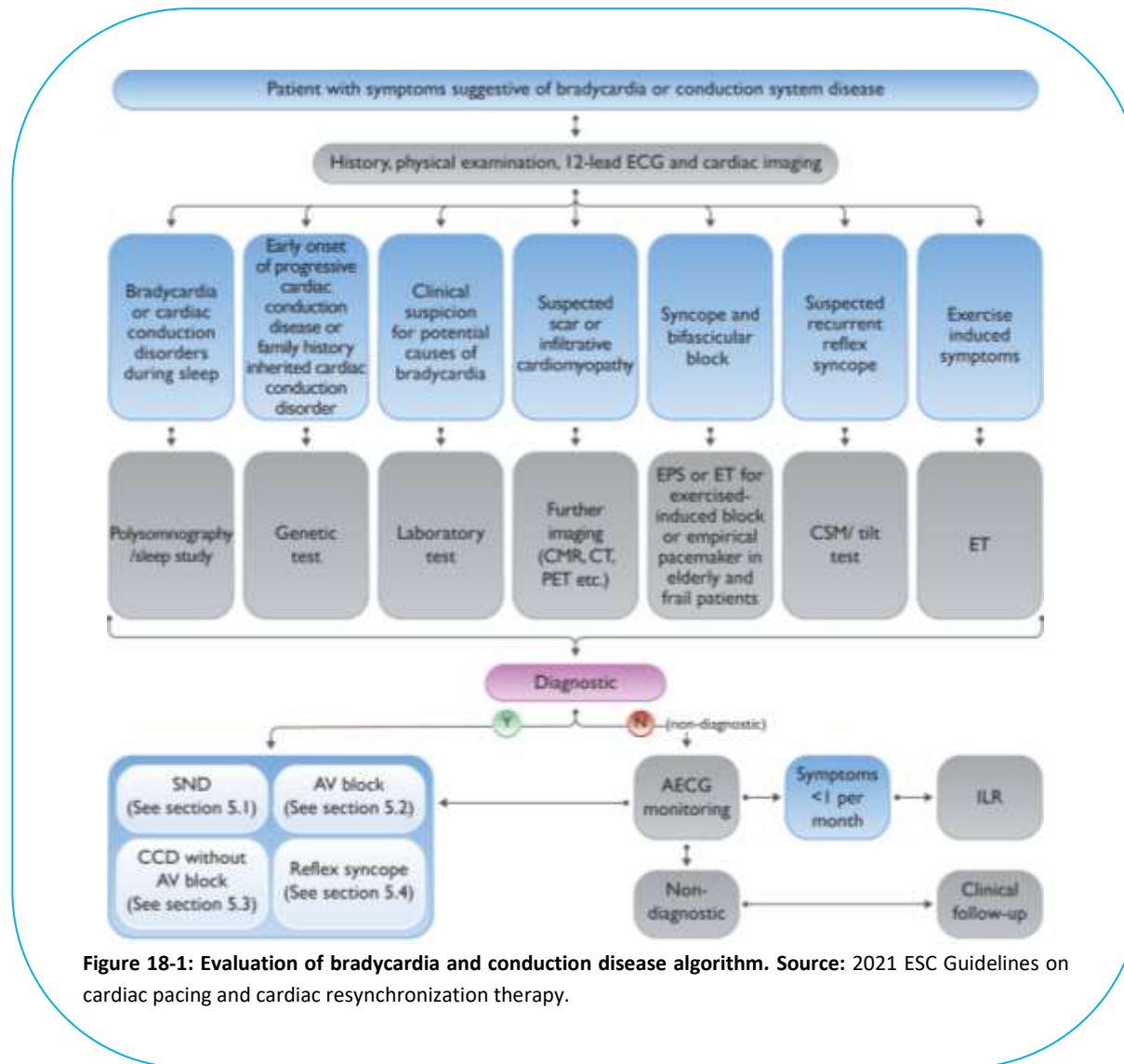


Figure 18-1: Evaluation of bradycardia and conduction disease algorithm. Source: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.

Sinus bradyarrhythmias

Causes:

- Idiopathic degenerative, age-related sinus node disease (most common cause).
- Acute ischemia may lead to transient SA block.
- Any chronic cardiomyopathy (e.g., ischemic, hypertensive, dilated) may lead to scarring of the SA node.
- Drugs.
- Hyper- or hypokalemia, hypothyroidism, obstructive jaundice.
- High vagal tone (athlete, acute gastric illness).
- Severe hypertension may stimulate the carotid sinus baroreceptors and lead to a reflex bradycardia (the converse of hypotension and reflex tachycardia).

Indications of Pacing:

Pacing for asymptomatic sinus node disease (SND) has never been shown to affect prognosis, as opposed to pacing for AVB. Therefore, SND can be considered as an appropriate indication for permanent pacing only when bradycardia due to SND is symptomatic. Establishing a correlation between symptoms and bradyarrhythmia is a crucial step in decision-making. However, age, concomitant heart disease, and other comorbidities may pose difficulties in establishing a clear cause effect relationship between SND and symptoms ⁽¹⁾. In patients investigated for syncope in whom asymptomatic pause(s) > 6 sec due to sinus arrest are eventually documented, pacing may be indicated.

(1) Beware that a vasovagal mechanism may lead to severe bradycardia <40 bpm and long pauses> 3 sec, sometimes a complete nodal AV block. In fact, syncope coinciding with long pauses or severe sinus bradycardia is more often secondary to a vasovagal mechanism than conduction disease. In vasovagal mechanism, symptoms and hypotension generally precede the rate slowing and pause, rather than follow them, and both the sinus rate and AV conduction diminish.

In patients with SND, controlled studies found that DDD was superior to single-chamber ventricular pacing in reducing the incidence of AF, stroke and the risk of pacemaker syndrome ⁽¹⁾. Potential exceptions are very elderly and/or frail patients with infrequent pauses who have limited functional capacity and/or a short, expected survival.

Table 18-6: ESC Recommendations for pacing in sinus node dysfunction:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Pacing is indicated in SND when symptoms can clearly be attributed to bradyarrhythmias.</i> | I | B |
| <i>Pacing may be considered in SND when symptoms are likely to be due to bradyarrhythmias, when the evidence is not conclusive.</i> | IIb | C |
| <i>In patients with syncope, cardiac pacing may be considered to reduce recurrent syncope when asymptomatic pause(s) > 6 s due to sinus arrest is documented.</i> | IIb | C |
| <i>In patients with SND and a DDD pacemaker, minimization of unnecessary ventricular pacing through programming is recommended.</i> | I | A |
| <i>Pacing is not recommended in patients with bradyarrhythmias related to SND that are asymptomatic or due to transient causes that can be corrected and prevented.</i> | III | C |
| <i>In patients who present chronotropic incompetence and have clear symptoms during exercise, DDD with rate-responsive pacing should be considered.</i> | IIa | B |
| <i>Pacing is indicated in symptomatic patients with the bradycardia-tachycardia form of SND in order to correct bradyarrhythmias and enable pharmacological treatment, unless ablation of the tachyarrhythmia is preferred.</i> | I | B |
| <i>In patients with the bradycardia-tachycardia variant of SND, programming of atrial ATP may be considered.</i> | IIb | B |

(1) Pacemaker syndrome is most commonly seen in the setting of a single chamber device with ventricular sensing and pacing lead. Since there is no atrial sensing lead to guide the ventricle, the ventricle contracts at the programmed rate regardless of the timing of atrial contraction. This leads to loss of AV synchrony which leads to back pressure in venous circulation systems that causes congestion (peripheral and pulmonary) as well as loss of atrial contribution leading to decreased cardiac output. VA conduction, which is usually a ventricular beat finding its way upwards to the atria also leads to a mistimed atrial contraction and produces similar effects.

AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic preautomaticity pauses after AF conversion, taking into account the clinical situation.

Ila

C

AV block

Causes:

- Idiopathic degenerative disease is the most common cause of AV block: **Lev disease** in the elderly (fibrosis of the left cardiac skeleton, with involvement of the mitral annulus and aortic valve), and **Lenegre disease** in the young (rapidly progressive sclerodegenerative disease).
- AV block may result from acute anterior or inferior ischemia, or chronic ischemic cardiomyopathy with diffuse myocardial fibrosis.
- Calcific valvular disease.
- Any cardiomyopathy can affect the conduction system. Varying degrees of AV blocks are seen in up to 15% of dilated cardiomyopathies (particularly acute myocarditis and Chagas disease); in infiltrative cardiomyopathies (particularly sarcoidosis of the young); and in some connective tissue disorders (lupus, ankylosing spondylitis).
- Drugs (β -blockers, calcium antagonists, digoxin, and antiarrhythmic drugs).
- Electrolytes (hypo- or hyperkalemia, hypermagnesemia).
- High vagal tone (sleep, vomiting, cough, athlete's heart) may lead to AV block at the nodal level. This includes sleep apnea. Also, athletes may have AV Wenckebach, especially at night.
- AV block after cardiac surgery (mainly congenital heart disease surgery, in which AV block resolves in 2/3 of the cases; or, less commonly, valvular surgery). AV block usually resolves within 7 days, if at all.
- Lyme disease leads to a reversible AV nodal block. This AV block may take months to resolve and *is a form of nodal AV block that paradoxically worsens with exercise, leading to significant exercise limitation*. Diagnosis is suggested by the context (outdoor exposure in endemic areas, tick bites, erythema migrans in the last 1–2 months) and established by serology.

N.B: Causes of AV block in the young:

- Benign vagotonic AV nodal block during sleep (particularly athletes) or during vasovagal syncope
- Sarcoidosis and other autoimmune diseases (lupus, ankylosing spondylitis)
- Lyme disease
- Myocarditis and Chagas disease
- Inherited channelopathies, particularly Lamin A/C mutation, which also leads to dilated cardiomyopathy, and SCN5A mutation.
- Congenital AV block: it may be inherited or secondary to fetal exposures (maternal lupus antibodies, toxins). It may appear in the neonatal period or later, in adulthood.

Effect of atropine and exercise on AV block:

| Table 18-7: Effect of atropine and exercise on AV block: | |
|--|---|
| AV nodal block | <i>Conduction ratio improves (AV has rich autonomic innervation and is affected by cholinergic and sympathetic effects)</i> |
| Infranodal block | <i>Conduction ratio remains unchanged or worsens ⁽¹⁾, as His and purkinjie conduction is not directly affected by the cholinergic or sympathetic system.</i> |

Indications of Pacing:

Treatment of AVB aims at improving the symptoms and preventing syncope and sudden cardiac death.

- **First-degree AV block:** Usually the prognosis is good in the absence of structural heart disease, and progression to high-degree block is uncommon. The indication for pacing relies on an established correlation between symptoms and AVB. There is weak evidence to show that marked PR prolongation (i.e. ≥ 300 ms), particularly when it persists or is prolonged during exercise, can lead to symptoms similar to pacemaker syndrome and/or that these can improve with pacing. Symptom correlation is crucial.

(1) *The increase in sinus rate leads to more atrial depolarizations reaching the infranodal area. Many of these atrial depolarizations partially penetrate the infranodal area without getting conducted all the way, thus preventing subsequent beats from getting conducted (extended refractory period). This is concealed conduction= blocked P waves prevent the conduction of subsequent P waves. A slower atrial rate is more likely to get conducted.*

- **Mobitz type I or Wenckebach:** In addition to the presence or absence of symptoms, the risk of progression to higher degrees of AVB should be considered. Supranodal block has a benign course, and the risk of progression to type II or a higher degree of AV block is low.
- **Mobitz type II, 2:1, and advanced AV block and third-degree AV block:** In the absence of a reversible cause, patients should receive a pacemaker even in the absence of symptoms.
- **Paroxysmal AV block:** Because of the risk of syncope and SCD and of the potential progression to permanent AVB, the indications for pacing are the same for paroxysmal as for permanent AVB. It is crucial to exclude reversible cause and to recognize the reflex forms of AVB, which may not need pacing.
- **AV block in the case of permanent AF:** In the absence of a potentially reversible cause, bradycardia or inappropriate chronotropic response (due to either intermittent or complete AVB) associated or reasonably correlated with symptoms is an indication for cardiac pacing. Any high-degree or infranodal block is also an indication for pacing, even in the absence of symptoms.

| Table 18-8: ESC Recommendations for pacing in AV block: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Pacing is indicated in patients in sinus rhythm or atrial arrhythmias with permanent or paroxysmal third- or second-degree type 2, infranodal 2:1, or high-degree AVB, irrespective of symptoms ⁽¹⁾.</i> | I | C |
| <i>In patients with permanent AF in need of a pacemaker, ventricular pacing with rate response function is recommended.</i> | I | C |
| <i>Pacing should be considered in patients with second-degree type 1 AVB that causes symptoms <u>or</u> is found to be located at intra- or infra-His levels at EPS.</i> | IIa | C |

(1) In asymptomatic narrow QRS complex 2:1 AVB, pacing may be avoided if supra-Hisian block is clinically suspected (concomitant Wenckebach is observed, and block disappears with exercise) or demonstrated at EPS.

| | | |
|---|------------|----------|
| <i>In patients with AVB, DDD should be preferred over single-chamber ventricular pacing to avoid pacemaker syndrome and to improve quality of life.</i> | Ila | A |
| <i>In patients with first-degree AVB (PR > 0.3 s), Permanent pacemaker implantation should be considered for patients with persistent symptoms similar to those of pacemaker syndrome and clearly attributable to the AVB.</i> | Ila | C |
| <i>Pacing is not recommended in patients with AVB due to transient causes that can be corrected and prevented.</i> | III | C |

Bundle branch blocks

Blood supply: The right bundle and the left anterior fascicle are long and slender and have a single blood supply (LAD); this makes these structures vulnerable to injury or to the aging process earlier than the left bundle. The main left bundle and the posterior fascicle are short and thick, and both have dual blood supply (LAD and RCA); this makes those structures less vulnerable to injury.

RBBB:

- RBBB and LAFB are common in the general population, and in patients without any underlying heart disease (results from a benign focal degeneration of the slender right bundle).
- Transient RBBB is the most common block after cardiac contusion or cardiac compressions.
- *If RBBB occurs in LV systolic dysfunction, it will be at least as malignant as LBBB and is more frequently associated with ischemic cardiomyopathy and a large scar burden than LBBB, more specifically a large anteroseptal scar* (The right bundle is supplied by the first septal branch, and thus RBBB may result from proximal LAD occlusion).

LBBB:

- The left bundle has dual supply, and thus LBBB does not usually result from an ischemic scar but from LV dilatation or hypertrophy (the increased wall stress and the patchy myocardial fibrosis lead to strain, fibrosis, and calcification of the left

bundle). If LBBB is ischemic in origin, it is associated with extensive CAD). LBBB rarely results from acute infarction, and if it does, it is usually a large infarction involving both the LAD and RCA territories.

- Only 11% have no apparent heart disease. Even in the absence of obvious heart disease during the initial evaluation, an isolated LBBB is associated with cardiac disease during follow-up.
- LBBB is associated with an increase in the long-term mortality, MI, and sudden death, even in relatively young (45–55 years) and asymptomatic patients without obvious cardiac disease. In addition, LBBB may induce dyssynchrony, abnormal diastolic function, and reduced LVEF.

In light of this pathophysiology, LBBB, RBBB, bi- and trifascicular block can be due to:

- o **Degeneration of the conduction system**, particularly in the case of RBBB. In this setting, RBBB is twice as common as LBBB, and the prevalence of both increases with age and male sex. The prevalences of LBBB and RBBB are ~0.4% and 1%, respectively, at age 50 **vs.** 6% and 10%, respectively, at age 80.
- o **Underlying heart disease** such as ischemic cardiomyopathy, hypertensive cardiomyopathy, or any cardiomyopathy (valvular, dilated, hypertrophic, and infiltrative). In these cases, a bundle branch block (BBB) is a sign of diffuse myocardial disease, with scarring and slowing of conduction through a dilated or hypertrophied myocardium rather than a discrete bundle branch delay. It is often preceded by LVH, RVH, or incomplete blocks on ECG, has more left or right axis deviations and *may be > 150 ms, which is unusual with a discrete bundle block*.

It is associated with a worse cardiomyopathy prognosis and a reduced long-term survival. RBBB and LBBB have the same adverse independent prognostic value (worse mortality predictor in several studies).

In patients with severe HF who qualify for CRT, RBBB is associated with a poor response to CRT, and thus a worse prognosis and a higher mortality than LBBB.

Beside their established prognostic value in acute MI, both RBBB and LBBB are independent prognostic markers in patients with underlying chronic stable CAD and imply extensive CAD and worse LV function.

N.B: While LBBB or RBBB may be solely due to disease of the bundle branch rather than myocardial disease, a non-specific intraventricular conduction delay (IVCD) > 110 ms often signifies underlying myocardial disease with intramyocardial slowing of

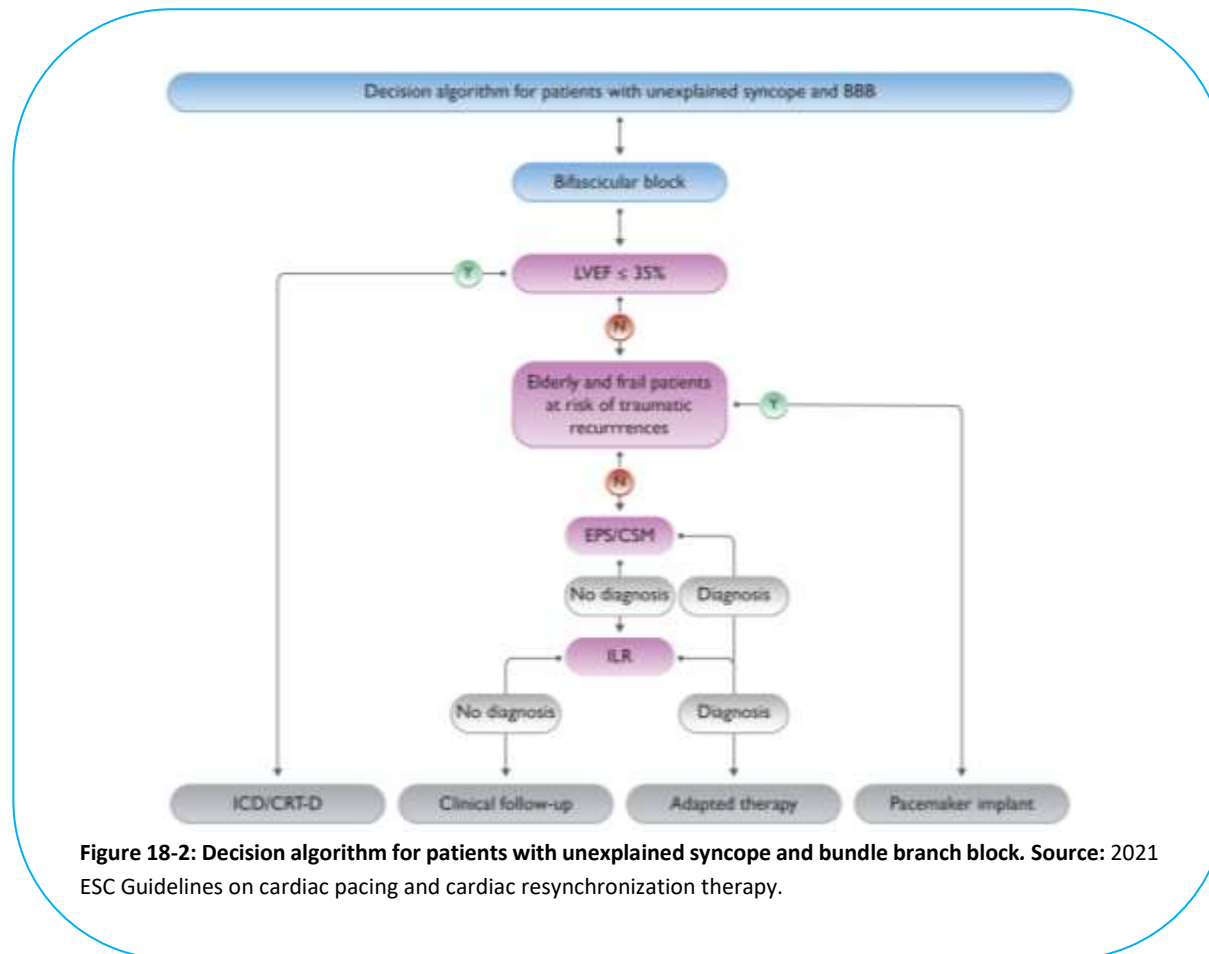
conduction. The disease may be subclinical and the echocardiogram may be normal. Baseline IVCD was associated with higher mortality than LBBB over the long-term follow-up of relatively young individuals with unsuspected heart disease (45–55 years of age).

Workup:

- *Perform an echocardiogram to evaluate RBBB or LBBB. If there is no evidence of a cardiomyopathy and no clinical suggestion of CAD, the bundle branch block is most likely isolated and related to a degeneration of the conduction system and, in the case of RBBB, does not usually portend an impaired prognosis.*
- Perform ischemic evaluation with stress testing for any possible angina equivalent (fatigue, dyspnea), especially in LBBB.
- Although innocent congenital aberration of the conduction system is possible, *isolated right heart pathologies or subclinical myocardial disease should be sought in a young patient (< 50) with RBBB: ASD, ARVD, sarcoidosis, Chagas disease.*

Indications of Pacing:

In patients with unexplained syncope and bifascicular block (*defined as LBBB or the combination of RBBB and with LAFB or LPF*), EPS is highly sensitive in identifying patients with intermittent or impending high-degree AVB. However, a negative EPS cannot rule out intermittent/paroxysmal AVB as the cause of syncope. Indeed, in patients with a negative EPS, intermittent or stable AVB was documented by ILR in 50% of cases. Therefore, elderly patients with bifascicular block and unexplained syncope might benefit from an empirical pacemaker (especially in unpredictable and recurrent syncope that exposes the patient to a high risk of traumatic recurrences, based on individual risk benefit evaluation).



▪ **Alternating bundle branch block:**

- This is an alternation of RBBB and LBBB on the same ECG or, much more commonly, on several ECGs obtained several days, months, or years apart. It may occur in two forms:
 - The baseline QRS is narrow, some ECGs show RBBB, while others show LBBB; this pattern is more concerning, as complete BBB is developing alternately over each bundle, and it may be a stronger incentive for pacemaker implantation.

- Some patients have incomplete block of one bundle, e.g., left bundle and intermittent complete block of the right bundle, the baseline ECG shows LBBB, but during deceleration or acceleration, RBBB develops and conduction occurs over the slow, but not completely blocked, left bundle. Depending on the refractory period of the right bundle, conduction may resume over the right bundle intermittently on the same ECG, or may resume once the trans-septal activation is delayed enough to allow the right bundle to recover.
- The risk of progression to complete AV block is higher than with unilateral BBB. Therefore, pacemaker implantation is warranted even in asymptomatic patients.

| Table 18-9: ESC Recommendations for pacing in patients with bundle branch block: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Pacing is indicated in patients with alternating BBB with or without symptoms.</i> | I | C |
| <i>In patients with unexplained syncope and bifascicular block, a pacemaker is indicated in the presence of either: (i) a baseline HV of ≥ 70 ms, (ii) second- or third-degree intra- or infra-Hisian block during incremental atrial pacing, (iii) abnormal response to pharmacological challenge.</i> | I | B |
| <i>Pacing may be considered in selected patients with unexplained syncope and bifascicular block without EPS (elderly, frail patients, high-risk and/or recurrent syncope).</i> | IIb | B |
| <i>Pacing is not recommended for asymptomatic BBB or bifascicular block.</i> | III | B |

- **Tachycardia or acceleration-dependent bundle branch block:**
 - Aberration may be induced in normal individuals when tachycardia occurs beyond a certain rate or premature excitation occurs at a very short R–R interval, particularly when the preceding R–R interval is long (Ashman’s phenomenon). This **physiologic** aberration is more likely to affect the right bundle, which has a longer refractory period than the left bundle. It may be seen with extreme heart rates (e.g., SVT with rate > 150 bpm), or may be initiated by a very premature beat having a long-short sequence.

- On the other hand, rate-related BBB occurring at lower rates (< 130 bpm) or longer R-R cycles is often **pathologic** and implies an underlying bundle branch disease. In these patients, the aberration may be LBBB or RBBB (more commonly LBBB) and it has the same diagnostic and prognostic value as BBB seen at rest. During tachycardia, the diseased bundle has less time to recover from its long refractory period and subsequently blocks.

- **Bradycardia or deceleration-dependent bundle branch block:**

With bradycardia, spontaneous diastolic (phase 4) depolarization may occur in a diseased His-Purkinje system or bundle branch. This depolarization may create a concealed action potential that prevents propagation of supraventricular impulses. Deceleration block implies significant underlying bundle branch disease and infranodal disease. In addition, these patients usually have tachycardia-dependent BBB, and the heart-rate range of normal conduction may be extremely narrow (e.g., 55–75 bpm), and inversely related to the amount of bundle injury.

Deceleration block implies significant underlying bundle branch disease and infranodal disease.

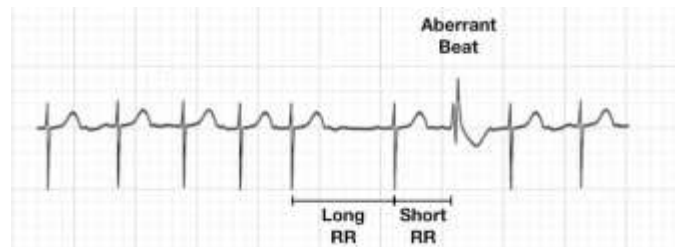


Figure 18-3: Ashman phenomenon. In 1947, Gouaux and Ashman reported that in AF, when a relatively long cycle was followed by a relatively short cycle, the beat with a short cycle often has RBBB morphology. **Mechanism:** The refractory period of the His-Purkinje system is proportional to the RR interval of the preceding beat. So, when two beats are separated by a long RR interval, the subsequent refractory period will be relatively long. If a premature supraventricular stimulus (short RR interval) follows a long RR interval whilst the His-Purkinje system is still refractory, then the conducted beat will appear abnormal. As the refractory period of the right bundle is slightly longer than the left, the aberrantly-conducted beat typically demonstrates a RBBB morphology.

Reflex syncope

Indications of Pacing:

In patients with reflex syncope, cardiac pacing should be the last resort and is only recommended in highly selected patients with reflex syncope (i.e. those > 40 years of age with severe recurrent unpredictable syncopal episodes when asystole has been documented, induced by either CSM or tilt testing, or recorded through a monitoring system).

There is sufficient evidence that DDD pacing should be considered in order to reduce recurrence of syncope in patients with dominant cardioinhibitory CSS (spontaneous syncope in presence of asystolic pause > 3 s during CSM) and in those in whom there is a correlation between spontaneous symptoms and ECG who are > 40 years of age and have severe recurrent unpredictable syncope.

There is weak evidence that DDD may be useful in reducing recurrences of syncope in patients with the clinical features of adenosine sensitive syncope.

| Table 18-10: ESC Recommendations for pacing for reflex syncope: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Dual-chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged > 40 years, with severe, unpredictable, recurrent syncope who have: <ul style="list-style-type: none">○ Spontaneous documented symptomatic asystolic pause(s) > 3 s <u>or</u>○ asymptomatic pause(s) > 6 s due to sinus arrest or AVB; <u>or</u>○ Cardioinhibitory carotid sinus syndrome; <u>or</u>○ Asystolic syncope during tilt testing. | I | A |
| Dual-chamber cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope (adenosine induced AV block > 10 s). | IIb | B |
| Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex. | III | B |

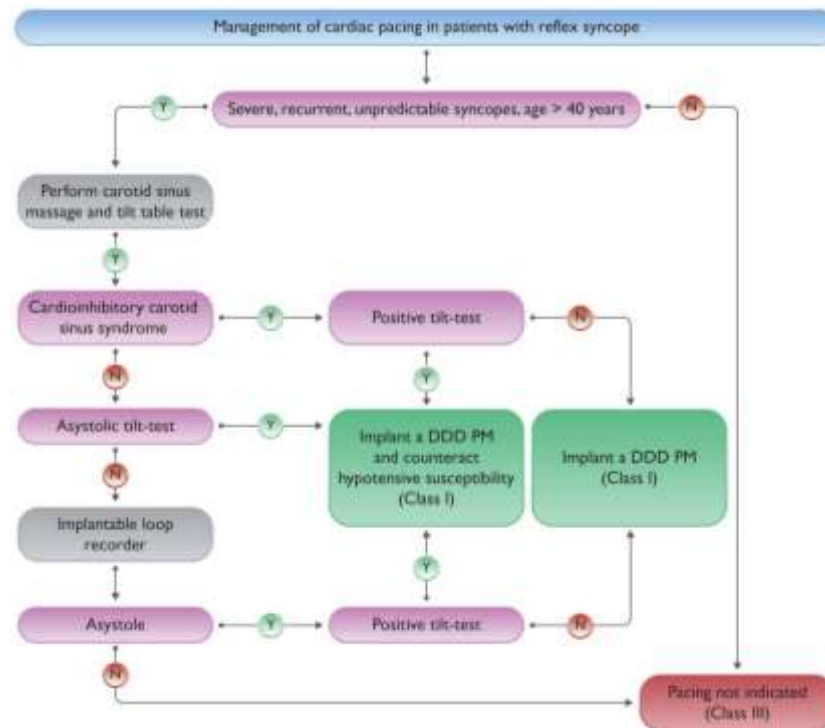
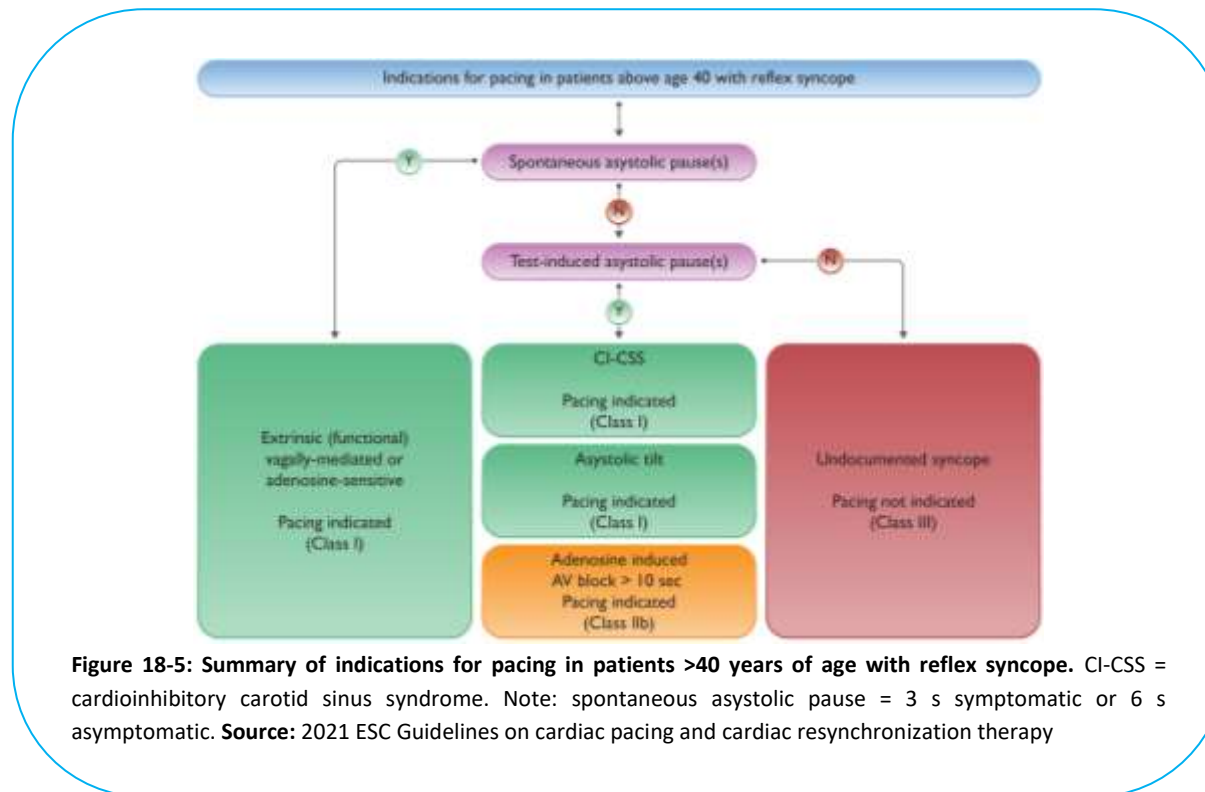


Figure 18-4: Decision pathway for cardiac pacing in patients with reflex syncope. Cardioinhibitory carotid sinus syndrome is defined when the carotid sinus massage results in spontaneous syncope in presence of asystolic pause > 3 s. Asystolic tilt positive test is defined when the tilt table test results in spontaneous syncope in presence of asystolic pause > 3 s. Asystole detected by ILR: symptomatic asystolic pause(s) > 3 s or asymptomatic pause(s) > 6 s due to sinus arrest, AV block, or the combination of the two. Source: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.



Suspected (undocumented) bradycardia

Table 18-11: ESC Recommendations for cardiac pacing in patients with suspected (undocumented) syncope and unexplained falls:

| Recommendations | Class | Level |
|---|------------|----------|
| <i>In patients with recurrent unexplained falls, the same assessment as for unexplained syncope should be considered.</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>Pacing is not recommended in patients with unexplained falls in the absence of any other documented indication.</i> | III | B |
| <i>Pacing is not recommended in patients with unexplained syncope without evidence of SND or conduction disturbance.</i> | III | C |

Indications for pacing in specific conditions

▪ **Pacing in acute MI:**

In patients with acute MI, significant bradyarrhythmia may occur due to autonomic influences **or** damage of the conduction system by ischaemia and/or reperfusion. Most often it resolves within a few days (Sick sinus syndrome after occlusion of the RCA resolves in most cases).

If AV block does not resolve within 10 days, a permanent pacemaker should be implanted. In the absence of robust scientific data, the waiting period before pacemaker implantation has to be decided individually. It may last up to 10 days but can be shortened to 5 days depending on the occluded vessel, time delay, and success of revascularization.

Conditions favouring earlier pacemaker implantation include: unsuccessful or late revascularization, anterior MI, bifascicular or AV block before MI, and progression of AVB within the first days after MI.

If revascularization is incomplete, pacemaker implantation can usually still be postponed and implantation only be performed if symptoms due to sinus bradycardia persist.

Table 18-12: ESC Recommendations for cardiac pacing after acute myocardial infarction:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|---------------------|---------------------|
| <i>Implantation of a permanent pacemaker is indicated with the same recommendations as in a general population when AVB does not resolve within a waiting period of at least 5 days after MI.</i> | I | C |

| | | |
|--|------------|----------|
| <i>In selected patients with AVB in the context of anterior wall MI and acute HF, early device implantation (CRT-D/CRT-P) may be considered.</i> | IIb | C |
| <i>Pacing is not recommended if AVB resolves after revascularization or spontaneously.</i> | III | B |

▪ **Pacing after cardiac surgery and heart transplantation:**

| Table 18-13: ESC Recommendations for cardiac pacing after cardiac surgery and heart transplantation: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| 1) High-degree or complete AVB after cardiac surgery: <i>A period of clinical observation of at least 5 days is indicated to assess whether the rhythm disturbance is transient and resolves. However, in the case of complete AVB with low or no escape rhythm when resolution is unlikely, this period can be shortened.</i> | I | C |
| 2) Surgery for valvular endocarditis and intraoperative complete AVB: <i>Immediate epicardial pacemaker implantation should be considered in patients with surgery for valvular endocarditis and complete AVB if one of the following predictors of persistence is present: pre-operative conduction abnormality, Staph aureus infection, intracardiac abscess, tricuspid valve involvement, or previous valvular surgery.</i> | IIa | C |
| 3) SND after cardiac surgery and heart transplantation: <i>Before permanent pacemaker implantation, a period of observation of up to 6 weeks should be considered.</i> | IIa | C |
| 4) Chronotropic incompetence after heart transplantation: <i>Cardiac pacing should be considered for chronotropic incompetence persisting for > 6 weeks after heart transplantation to improve quality of life.</i> | IIa | C |
| 5) At the time of tricuspid valve surgery: | IIa | C |

- *When ventricular pacing is indicated, transvalvular leads should be avoided and transvenous implantation of a coronary sinus lead or epicardial ventricular leads should be considered.*
- *During tricuspid valve surgery, removal of pre-existing transvalvular leads should be considered and preferred over sewing in the lead between the annulus and a bioprosthesis or annuloplasty ring.*
- *In the case of isolated tricuspid annuloplasty, a preexisting RV lead may be left in place without jailing it between ring and annulus based on an individual risk benefit analysis.*

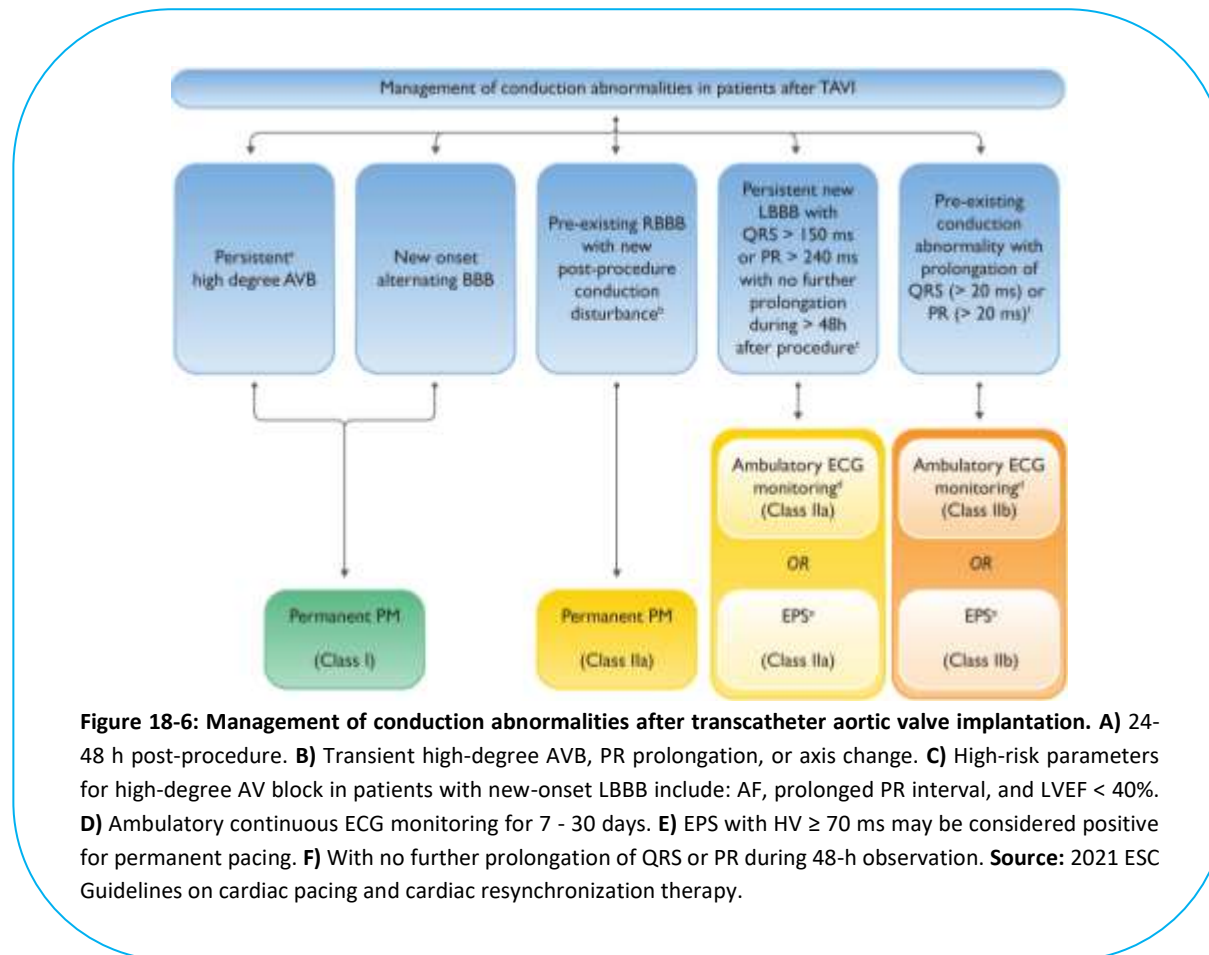
▪ **Pacing after TAVI:**

Rates of permanent pacemaker implantation after TAVI range between 3.4-25.9%. Whereas the association between pacing after TAVI and outcome is controversial, RV pacing may lead to deterioration in LV function. Thus, efforts to minimize unnecessary permanent pacing are warranted.

Predictors for permanent pacing (especially RBBB) should be incorporated into procedural planning including transcatheter heart valve selection, implantation height, and balloon inflations.

| Table 18-14: Predictors for permanent pacing after TAVI: |
|---|
| ECG: |
| <i>Right BBB (the most powerful predictor for permanent pacemaker implantation)</i> |
| <i>PR-interval prolongation</i> |
| <i>Left anterior hemiblock.</i> |
| Patient: |
| <i>Older age (per 1-year increase)</i> |
| <i>Male sex</i> |
| <i>Larger BMI (per 1-unit increase)</i> |
| Anatomical: |

| |
|---|
| <i>Severe mitral annular calcification</i> |
| <i>LVOT calcifications</i> |
| <i>Membranous septum length</i> |
| <i>Porcelain aorta</i> |
| <i>Higher mean AV Pressure gradient</i> |
| Procedural: |
| <i>Self-expandable valve</i> |
| <i>Deeper valve implantation</i> |
| <i>Larger ratio between prosthesis diameter versus annulus or LVOT diameter</i> |
| <i>Balloon post-dilatation</i> |
| <i>TAVI in valve-in-valve vs. native valve procedure</i> |



| Table 18-15: ESC Recommendations for cardiac pacing after TAVI: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Permanent pacing is recommended in patients with: | | |

| | | |
|---|-----|---|
| - complete or high-degree AVB that persists for 24 - 48 h after TAVI. | I | B |
| - new-onset alternating BBB after TAVI. | I | C |
| Early ⁽¹⁾ permanent pacing should be considered in patients with pre-existing RBBB who develop any further conduction disturbance during or after TAVI. ⁽²⁾ | IIa | B |
| Ambulatory ECG monitoring ⁽³⁾ or EPS ⁽⁴⁾ : | | |
| - should be considered for patients with new LBBB with QRS > 150 ms or PR > 240 ms with no further prolongation during the > 48 h after TAVI. | IIa | C |
| - may be considered for patients with a pre-existing conduction abnormality who develop prolongation of QRS or PR > 20 ms ⁽⁵⁾ . | IIb | C |
| Prophylactic permanent pacemaker implantation is not indicated before TAVI in patients with RBBB and no indication for permanent pacing. | III | C |

▪ **Cardiac pacing and CRT in congenital heart disease:**

Permanent pacing in patients with moderate or complex CHD should be performed in centres with a multidisciplinary team and expertise in CHD-related device therapy. Generally, decision-making for pacemaker therapy in patients with CHD is based on expert consensus and individual evaluation due to lack of evidence from RCTs.

In the presence of an intracardiac shunt between the systemic and pulmonary circulation, endovascular lead placement is relatively contraindicated due to the risk of arterial embolism.

(1) Immediately after procedure or within 24 h.

(2) Transient high-degree AVB, PR prolongation, or QRS axis change.

(3) Ambulatory continuous ECG monitoring (implantable or external) for 7-30 days.

(4) EPS should be performed ≥ 3 days after TAVI. HV ≥ 70 ms may be considered positive for permanent pacing.

(5) With no further prolongation of QRS or PR during 48-h observation.

Note: CRT in patients requiring pacing after TAVI has the same indication as for general patients

Standard indications for CRT may be considered in CHD, taking into account that the anatomy, morphology of the systemic ventricle, and cause of dyssynchrony, as well as QRS morphology, may be atypical.

| Table 18-16: ESC Recommendations for cardiac pacing in patients with congenital heart disease: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>In patients with congenital complete or high-degree AVB, pacing is recommended if one of the following risk factors is present:</i> A. Symptoms B. Pauses > 3 the cycle length of the ventricular escape rhythm C. Broad QRS escape rhythm. D. Prolonged QT interval E. Complex ventricular ectopy F. Mean daytime heart rate < 50 b.p.m. | I | C |
| <i>In patients with congenital complete or high-degree AVB, permanent pacing may be considered even if no risk factors are present.</i> | IIb | C |
| <i>In patients with persistent post-operative bifascicular block associated with transient complete AVB, permanent pacing may be considered.</i> | IIb | C |
| <i>In patients with complex CHD and asymptomatic bradycardia (awake resting heart rate < 40 b.p.m. or pauses > 3 s), permanent pacing may be considered on an individual basis.</i> | IIb | C |

▪ **Pacing in hypertrophic cardiomyopathy:**

In patients with symptoms caused by LVOT obstruction, treatment options include drugs, surgery, septal alcohol ablation, and AV sequential pacing with a short AV delay ⁽¹⁾.

AV sequential pacing with a short AV delay may be considered if the patients are unsuitable or unwilling to undergo invasive septal reduction therapy or if the patients already have a pacemaker or ICD for other indication. Otherwise, standard criteria for CRT and pacing are recommended in patients with HCM. Pacing parameters should be optimized to achieve maximum pre-excitation of the RV apex with minimal compromise of LV filling (typically achieved with a resting sensed AV interval of 100 ± 30 ms).

| Table 18-17: ESC Recommendations for cardiac pacing in hypertrophic obstructive cardiomyopathy: | | |
|--|------------|----------|
| Recommendations | Class | Level |
| <p><i>AV sequential pacing with short AV delay may be considered in patients with drug refractory symptoms, ≥ 50 mmHg baseline or provokable LVOT gradient, in sinus rhythm, who:</i></p> <ul style="list-style-type: none"> <i>- have other pacing or ICD indications.</i> <i>- Are unsuitable for or refusing other invasive septal reduction therapies.</i> <i>- Are at high risk of developing AVB during septal ablation.</i> | IIb | B |

▪ **Pacing in rare diseases:**

- **Long QT syndrome:** There are multiple inter-relationships between the different forms of long QT syndrome (LQTS) and bradycardia: **(i)** LQTS can be associated with sinus bradycardia; **(ii)** very long ventricular myocardial refractory periods can cause

(1) The mechanism of action of AV sequential pacing is not completely elucidated. Hypotheses to explain the beneficial effects include: **(i)** negative inotropic effect and reduced hypercontractility of the LV, **(ii)** asynchronous septal activation and delayed septal thickening, **(iii)** limitation of abnormal mitral valve motion, **(iv)** interaction with LV filling, and **(v)** ventricular remodelling.

Diastolic dysfunction with impaired LV filling is commonly observed in HCM and contributes largely to symptoms. Too short AV delays create left AV dyssynchrony which reduces the atrial contribution to LV filling. Preserving optimal LV filling through a fully efficient left atrial systole is thus crucial to ensure optimal result by pacing.

2:1 AVB; **(iii)** sudden rate changes can trigger torsades de pointes tachycardia; and **(iv)** treatment with beta-blockers to suppress sympathetic triggers of torsades de pointes may cause bradycardia.

As current ICDs provide all pacemaker functions, a standalone pacemaker is rarely indicated in LQTS.

Pacemaker instead of ICD implantation represents a treatment option in:

- Neonates and small infants with LQTS.
- LQTS patients with symptomatic bradycardia (spontaneous or due to beta blockers) if ventricular tachyarrhythmias are unlikely or if ICD implantation is not desired (e.g. patient preference).

○ **Neuromuscular diseases:**

Neuromuscular diseases are a group of heterogeneous inherited disorders affecting the skeletal muscle and frequently also involve the heart. The recommendations present guidance in the instances where the recommendations for cardiac pacing differ from those used for other patients with bradycardia.

Whenever pacing is indicated in neuromuscular disease, CRT and ICD indications should be considered according to relevant guidelines.

○ **Inflammatory diseases:**

Infections (viral, bacterial including Borreliosis, protozoa, fungal, parasites), autoimmune (e.g. giant cell myocarditis, sarcoidosis, rheumatic heart disease, connective tissue disease, eosinophilic myocarditis), toxic (alcohol, cocaine, cancer therapies, especially monoclonal antibodies), and physical reactions (radiation therapy) can cause inflammatory heart disease. Involvement of the AVN and the conduction system is more frequent than that of the sinus node. AVB may indicate involvement of the septum in the inflammatory process and is a predictor of adverse outcome. Before choosing a device type, the indication for an ICD and/or CRT rather than a single-chamber or DDD pacemaker should be considered because most causes of inflammatory disease-causing bradycardia may also result in reduced myocardial contractility and ventricular fibrosis.

| Table 18-18: ESC Recommendations for cardiac pacing in rare diseases: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Neuromuscular diseases: | | |

| | | |
|---|------------|----------|
| <i>Permanent pacing is indicated in patients with neuromuscular diseases (such as myotonic dystrophy type 1) and any second- or third-degree AVB <u>or</u> HV \geq 70 ms, with or without symptoms.</i> | I | C |
| <i>permanent pacemaker implantation may be considered in patients with neuromuscular disease (such as myotonic dystrophy type 1) with PR \geq 240 ms <u>or</u> QRS duration \geq 120 ms.</i> | IIb | C |
| Kearns Sayre syndrome ⁽¹⁾: | | |
| <i>Permanent pacing should be considered in patients with Kearns Sayre syndrome who have PR prolongation, any degree of AVB, BBB, or fascicular block.</i> | IIa | C |
| <i>Permanent pacing may be considered prophylactically in patients with Kearns Sayre syndrome without cardiac conduction disorder.</i> | IIb | C |
| LMNA gene mutations: | | |
| <i>ICD with pacing capabilities should be considered in patients with LMNA gene mutations (including Emery Dreifuss and limb-girdle muscular dystrophies) who fulfil conventional criteria for pacemaker implantation <u>or</u> who have prolonged PR interval with LBBB, if at least 1- year survival is expected.</i> | IIa | C |
| Cardiac sarcoidosis: | | |
| <i>In patients with cardiac sarcoidosis who have permanent or transient AVB, implantation of a device capable of cardiac pacing should be considered.</i> | IIa | C |
| <i>In patients with sarcoidosis and an indication for permanent pacing who have LVEF < 50%, implantation of a CRT-D should be considered.</i> | IIa | C |

(1) Kearns-Sayre syndrome (KSS) is a clinical subtype of chronic progressive external ophthalmoplegia (CPEO). KSS is defined by the following triad: **(i)** onset before the age of 20, **(ii)** CPEO, and **(iii)** pigmentary retinopathy. Affected individuals have at least 1 of the following conditions: complete heart block, CSF protein > 100 mg/dL, cerebellar ataxia, short stature, deafness, dementia, and endocrine abnormalities.

▪ **Temporary Pacing:**

Temporary pacing can provide electronic cardiac stimulation in patients with acute life-threatening bradycardia or can be placed prophylactically when the need for pacing is anticipated (e.g. after cardiac surgery). Modalities for emergency temporary pacing include transvenous, epicardial, and transcutaneous approaches.

| Table 18-19: ESC Recommendations regarding temporary cardiac pacing: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Temporary transvenous pacing is recommended in cases of hemodynamic-compromising bradyarrhythmia refractory to intravenous chronotropic drugs.</i> | I | C |
| <i>Transcutaneous pacing should be considered in cases of hemodynamic-compromising bradyarrhythmia when temporary transvenous pacing is not possible or available.</i> | IIa | C |
| <i>Temporary transvenous pacing should be considered:</i> <ul style="list-style-type: none"> ○ <i>When immediate pacing is indicated and pacing indications are expected to be reversible (such as in the context of myocardial ischemia, myocarditis, electrolyte disturbances, toxic exposure, or after cardiac surgery).</i> ○ <i>As a bridge to permanent pacemaker implantation when this procedure is not immediately available or possible due to concomitant infection.</i> | IIa | C |
| <i>For long-term temporary transvenous pacing, an active fixation lead inserted through the skin and connected to an external pacemaker should be considered.</i> | IIa | C |

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- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier
- <https://litfl.com/ecg-library/>

Chapter 19:

Cardiac Pacing

Permanent Pacemaker

Indications:

Table 19-1: Summary of permanent pacemaker indications:

Sinus node dysfunction with:

- Associated symptoms (can be clearly attributed to bradyarrhythmia)
- Symptomatic chronotropic incompetence.
- Symptomatic patients with the bradycardia-tachycardia.

AV block:

- Mobitz II AV block even if it is asymptomatic.
- High-grade or third-degree AV block, even if it is asymptomatic.
- Mobitz I or first-degree AV block leading to “pacemaker syndrome”-like symptoms ⁽¹⁾ or found to be located at intra- or infra-His levels at EPS.
- Asymptomatic, severely prolonged HV interval (His-ventricle) > 100 ms or infra-His block during incremental pacing on EP study.
- Any AV block (including Mobitz I) with associated symptomatic bradycardia (symptomatic means near-syncope/syncope, severe fatigue, or active HF concomitant to bradycardia) or symptomatic pauses.

Bundle branch blocks:

(1) This occurs with a very prolonged PR interval ($\geq 300\text{ms}$), which makes the P wave very close to the precedent QRS. AV synchrony is lost, and the atria sometimes contract against closed valves. On echo, E and A waves are fused, the diastolic filling time is reduced, and there is diastolic MR. Consequently, cardiac output is reduced and LA pressure is increased, which leads to fatigue, dyspnea, and syncope.

- Alternating BBB with or without symptoms.
- Bifascicular block and unexplained syncope in the presence of either: (i) a baseline HV of ≥ 70 ms, (ii) second- or third-degree intra- or infra-Hisian block during incremental atrial pacing, (iii) abnormal response to pharmacological challenge.

Reflex Syncope with:

Pacing is indicated to reduce recurrent syncope in patients aged > 40 years, who have:

- Symptomatic pause(s) > 3 s or asymptomatic pause(s) > 6 s due to sinus arrest or AVB; or
- Cardioinhibitory carotid sinus syndrome ⁽¹⁾; or
- Asystolic syncope during tilt testing ⁽²⁾

Other Conditions:

- Refractory dilated cardiomyopathy with QRS ≥ 130 ms (CRT).
- Drug refractory HOCM with contraindication to or refusing septal reduction therapy.
- High risk patients with congenital long QT syndrome.
- Symptomatic recurrent SVT terminated by pacing. When catheter ablation and/or drugs are ineffective.
- Sustained VT terminated by pacing.
- After heart transplantation for persistent symptomatic bradycardia or chronotropic incompetence.
- After TAVI if:
 - Complete or high-degree AVB that persists for 24 - 48 h after TAVI
 - New-onset alternating BBB after TAVI
 - Patients with pre-existing RBBB who develop any further conduction disturbance after TAVI ⁽³⁾.
- Congenital AV block *if* one of the following risk factors is present:
 - Symptoms

(1) Cardioinhibitory carotid sinus syndrome is defined when the carotid sinus massage results in spontaneous syncope in presence of asystolic pause > 3 s.

(2) Asystolic tilt positive test is defined when the tilt table test results in spontaneous syncope in presence of asystolic pause > 3 s.

(3) Transient high degree AV block, PR prolongation, or QRS axis change.

- Pauses > 3 the cycle length of the ventricular escape rhythm
- Broad QRS escape rhythm
- Prolonged QT interval
- Complex ventricular ectopy
- Mean daytime heart rate < 50 b.p.m.

All this in the absence of a reversible cause, such as drugs, electrolytes, high vagal tone, acute ischemia, or the immediate post-cardiac surgery state, in which a temporary transvenous PM may be indicated for temporary support. If the bradyarrhythmia does not resolve after treatment of these causes, especially in the case of an acute anterior MI, a permanent PM is indicated.

Types of cardiac rhythm devices:

Pacemakers (PMs) are designated by a five-letter code:

- **1st letter** = chamber paced: **A** (right atrium), **V** (right ventricle), or **D** (dual, both atrium and ventricle)
- **2nd letter** = chamber sensed: **A**, **V**, or **D**
- **3rd letter** = action taken by the PM when it senses an event: **I** (inhibits pacing), **T** (triggers pacing, like pacing V after sensing A), or **D**
- **4th letter (R)** = Rate modulation, which indicates a rate-response mode. A rate response means the device has accelerometer or ventilator sensors that increase the rate with activity.
- **5th letter** = Capability of multisite pacing: **A**, **V**, **D**, **O**.

Mode of Pacing:

- **Asynchronous Pacing (VOO, AOO, DOO):**

- Pacing without sensing.
- Not manufactured yet.
- **Single Chamber demand Pacing (VVI, AAI):**
 - Single sensing and pacing lead in RA (AAI) or RV (VVI).
 - In VVI, PM has a single sensing and pacing lead in the right ventricle. It paces the ventricle when it sees that the interval between two QRS complexes is longer than the back-up limit, called the *lower rate interval*; a limit of 1 second, for example, corresponds to a HR of 60 bpm.
 - It does not see or pace the atrium, and does not make the ventricle track the atrium. In patients with sinus rhythm, VVI may lead to AV dissociation and loss of the atrial contribution to the cardiac output.
 - VVI pacing is mainly used in chronic AF, wherein the atrium cannot be paced or tracked. It may also be an acceptable option in older sedentary patients with AV block.
 - VVI pacing may lead to a ***pacemaker syndrome***.
 Since there is no atrial sensing lead to guide the ventricle, the ventricle contracts at the programmed rate regardless of the timing of atrial contraction. This leads to loss of AV synchrony which leads to back pressure in venous circulation systems that causes congestion (peripheral and pulmonary) as well as loss of atrial contribution in stroke volume leading to decreased cardiac output. VA conduction, which is usually a ventricular beat finding its way upwards to the atria also leads to a mistimed atrial contraction and produces similar effects.
- **Dual Chamber Pacing and Sensing (DDD): = AAI + VAT + VVI**
 DDD is a dual-chamber PM, with sensing and pacing leads placed in both the RA and the RV.
 - PM tracks the P wave and paces the ventricle whenever a P wave is not followed by a ventricular activity. After a P wave, PM waits a certain time before pacing the ventricle; this time is the *programmed AV interval*. This function is the VAT function or AV sequential pacing: PM sees the atrium ("A") then triggers ("T") the ventricle ("V"). It will appropriately track sinus tachycardia up to a certain rate (upper tracking rate).
 - PM paces the atrium if P wave is absent (sinus node disease) and lets it spontaneously conduct to the ventricle (AAI function).

- PM sequentially paces the atrium then the ventricle in case of severe sinus node disease combined with severe AV block (AAI + VAT functions).

Perioperative management of pacemaker implantations:

| Table 19-2: ESC Recommendations regarding device implantations and peri-operative management: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Administration of pre-operative antibiotic prophylaxis within 1 h of skin incision is recommended to reduce risk of cardiovascular implantable electronic device (CIED) infection ⁽¹⁾ . | I | A |
| Chlorhexidine alcohol instead of povidone-iodine alcohol should be considered for skin antisepsis. | Ila | B |
| For venous access, the cephalic or axillary vein should be considered as first choice. | Ila | B |
| To confirm target ventricular lead position, use of multiple fluoroscopic views should be considered. | Ila | C |
| For implantation of coronary sinus leads, quadripolar leads should be considered as first choice. | Ila | C |
| Rinsing the device pocket with normal saline solution before wound closure should be considered. | Ila | C |
| In patients undergoing a reintervention CIED procedure, the use of an antibiotic-eluting envelope may be considered. | Ilb | B |

(1) The risk of infection is significantly reduced with a single dose of prophylactic antibiotic (cefazolin 1-2 g i.v. or flucloxacillin 1-2 g i.v.) given within 30-60 min [90-120 min for vancomycin (15 mg/kg)] before the procedure.

| | | |
|---|------------|----------|
| <i>Pacing of the mid-ventricular septum may be considered in patients at high risk of perforation (e.g. elderly, previous perforation, low body mass index, women).</i> | IIb | C |
| <i>In pacemaker implantations in patients with possible pocket issues such as increased risk of erosion due to low body mass index, Twiddler's syndrome, or for aesthetic reasons, a submuscular device pocket may be considered.</i> | IIb | C |
| <i>Heparin bridging of anticoagulated patients is not recommended.</i> | III | A |
| <i>Permanent pacemaker implantation is not recommended in patients with fever. Pacemaker implantation should be delayed until the patient has been afebrile for at least 24 h.</i> | III | B |

▪ **Management of anticoagulation in pacemaker procedures:**

| Table 19-3: Management of anticoagulation in pacemaker procedures: | | | | | |
|---|--|---|--|------------|--|
| | Dual antiplatelet therapy | | NOAC | VKA | OAC + antiplatelet |
| | Thrombotic risk after PCI | | | | |
| | Intermediate or low - > 1 month PCI - > 6 months ACS at index PCI | High - < 1 month PCI - < 6 months ACS at index PCI | | | |
| Low procedural bleeding risk <i>First implant</i> | Continue aspirin AND | Elective surgery: Consider postponement Otherwise: Continue DAPT | -Continue or interrupt as per operator preference. | Continue | Continue OAC. Discontinue antiplatelet per patient-specific |

| | | | | | |
|---|---|---|---|--|-----------------------|
| High procedural bleeding risk Device exchange, upgrade/revision procedure | Discontinue P2Y12 inhibitors before surgery: - Ticagrelor for 3 days - Clopidogrel for 5 days - Prasugrel for 7 days | Continue aspirin AND Discontinue P2Y12 inhibitors before surgery: -Ticagrelor for 3 days. -Clopidogrel for 5 days. -Prasugrel for 7 days. AND Bridging with GP IIb/IIIa inhibitors | - If interruption, then based on CrCl and specific NOAC | | risk/benefit analysis |
|---|---|---|---|--|-----------------------|

Selection of appropriate pacing mode:

- **In Sinus node disease:** DDD or AAI is superior to VVI pacing; as VVI pacing increased mortality (~1.5 times) in comparison to AAI pacing, and doubled the risk of AF and stroke (Danish randomized trial).
DDD pacemaker (with a programmed long AV interval) is preferred over AAI pacemaker due to the progressive risk of AV nodal disease over time.
- **In AV nodal disease:** DDD (vs. VVI) pacing reduces the incidence of AF and improves quality of life, through preservation of AV synchrony and LA pressure, without affecting mortality (UKPACE and CTOPP).

N.B: Regardless of the type of pacemaker used (DDD vs. VVI), ventricular pacing > 40% of the time increased the risk of AF and HF with a 3–4.5 times higher risk of HF hospitalization (MOST, MADIT and DAVID trials). Minimal ventricular pacing should be ensured; for example, program the AV interval as long as 250 ms after a sensed P wave to promote intrinsic ventricular activation.

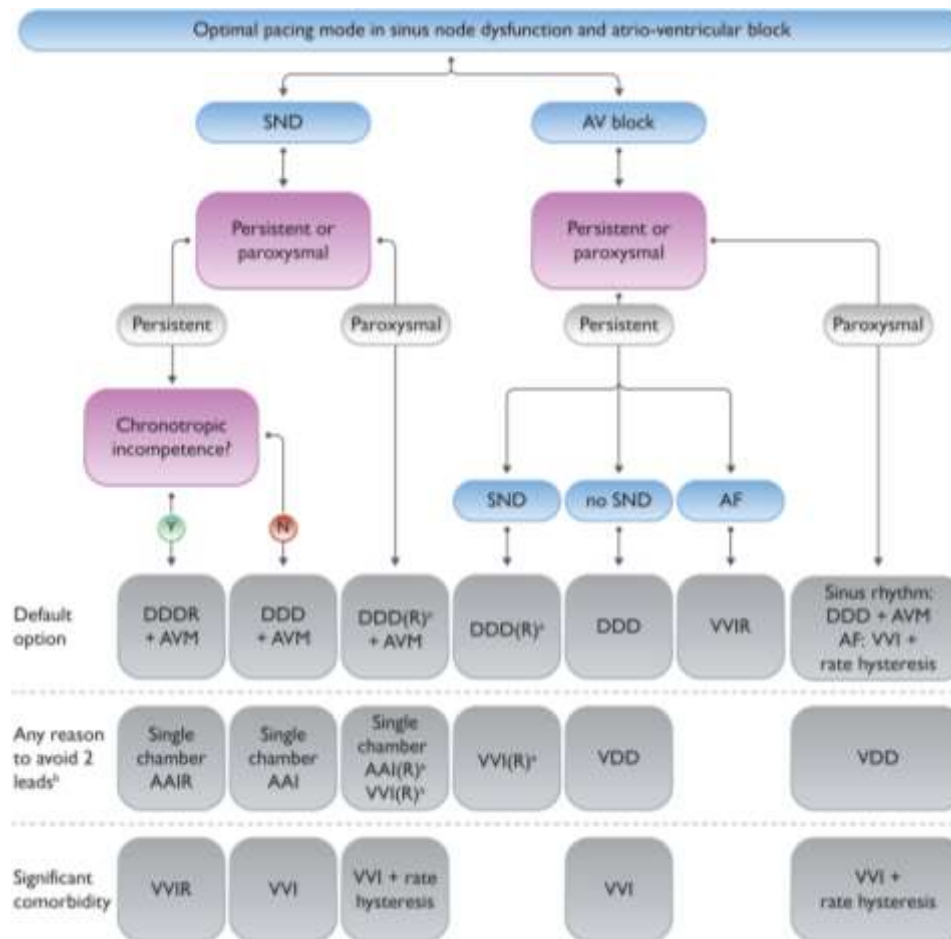


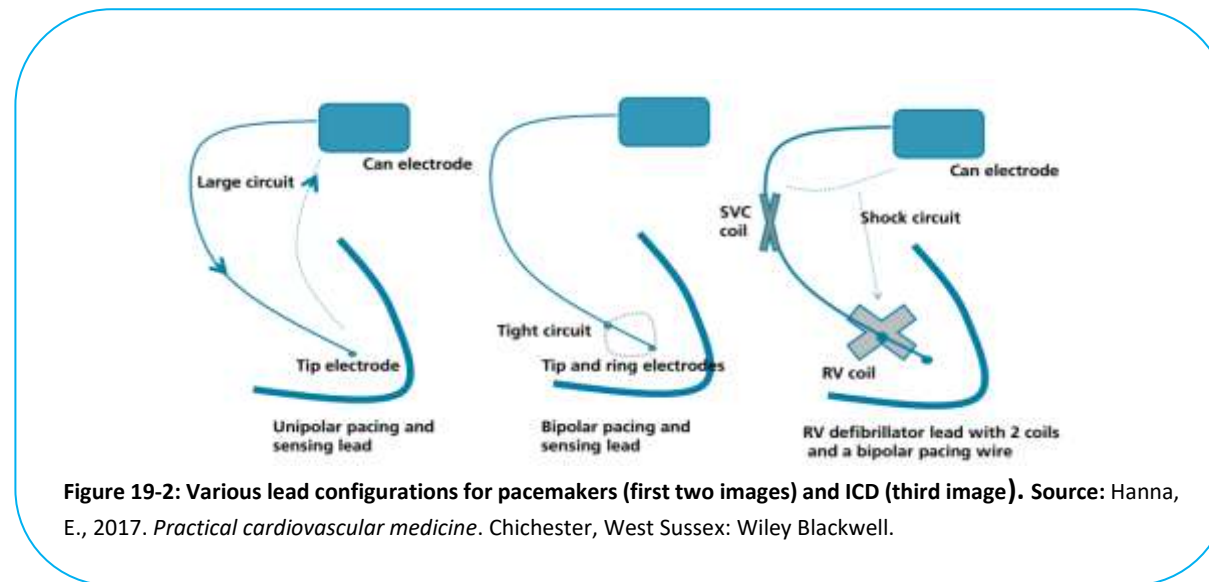
Figure 19-1: Optimal pacing mode and algorithm selection in sinus node dysfunction and atrioventricular block. AVM = atrioventricular management [i.e. AV delay programming (avoiding values > 230 ms) or specific algorithms to avoid/reduce unnecessary ventricular pacing]. **A)** (R) indicates that the programming of such a pacing mode is preferred only in the case of chronotropic incompetence. **B)** Reasons to avoid two leads include young age and limited venous access. **Note:** in patients who are candidates for a VVI/VDD pacemaker, a leadless pacemaker may be considered. **Source:** 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.

Leads:

Leads detect electrical activity between two electrodes (anode and cathode) and deliver the output current between these two electrodes:

- **Unipolar lead** has one electrode at the distal tip, the metal of the can constituting the other electrode. The pacing current flows through a large circuit and may cause stimulation of the chest muscle and a large pacing spike on the ECG. Also, the sensing current is large and is prone to sensing myopotentials.
- **Bipolar lead** has two electrodes on its distal end (ring and tip electrodes) creating a smaller sensing and pacing circuit. However, it has to contain two wires to conduct signals to and from both electrodes and needs to be slightly thicker. If the ring wire breaks, the lead converts to a unipolar mode.

A bipolar defibrillator lead contains two pacing electrodes and one or two defibrillator coils: one at the distal end (RV coil) ± one more proximal (SVC coil). After VT is sensed, the defibrillation circuit occurs between the can, which functions as an electrode, and the RV coil.



Generator placement on the left side allows delivery of energy that is orthogonal to the heart and traverses it more effectively. The current that flows through the lead and is delivered to the myocardium depends on both the battery voltage delivered and the lead resistance/impedance. In fact: $\text{Current (mA)} = \text{Voltage} / \text{Resistance}$.

The battery voltage is typically 2.8 volts. The lead itself needs to have a high impedance to reduce the current that is being drained. The lead tip needs to have a low resistance to allow electrical flow to the myocardium.

Upon new PM implantation, the pacing threshold rises over the first few weeks then goes down to a chronic baseline 8 weeks later. This is due to the initial inflammation at the lead tip and mandates programming of high pacing thresholds initially, followed by reprogramming 8 weeks later. A steroid-eluting lead prevents this phenomenon and allows chronically lower pacing thresholds.

Pacing leads are insulated, meaning they are covered with material that does not conduct electricity and prevents loss of current from the lead, allowing current to travel all the way to the myocardium.

Pacemaker Intervals:

- **VVI intervals:** A VVI pacemaker is characterized by two basic intervals:
 - **Lower rate interval** (the basic pacing rate) ⁽¹⁾.
 - **Ventricular refractory period**, during which the pacemaker cannot sense any signal or reset its timing based on signals.
- **DDD pacemaker's intervals:** A DDD pacemaker is characterized by four basic intervals:
 - **Lower rate interval** is the basic interval between paced P waves (the basic pacing rate). A hysteresis function may be established to delay the onset of atrial pacing.
 - **Ventricular refractory period** occurs after a sensed or paced ventricular event. This prevents the ventricular lead from sensing the residual energy from its own ventricular spike and from seeing and double-counting the QRS or the T wave.
 - **Post-ventricular atrial refractory period (PVARP)** begins immediately after the start of a ventricular event. An atrial activity falling in PVARP cannot initiate P-synchronous pacing. PVARP is meant to prevent: (i) sensing the ventricular activity by the atrial channel and tracking it (far-field), (ii) sensing and tracking a very premature PAC or a retrograde P wave occurring after a PVC.
 - **Programmed AV delay** from a sensed (intrinsic) or paced P wave. As opposed to the paced P wave, the PM senses an intrinsic P wave only after the atrial activity has spread for some time; therefore, the sensed AV interval is programmed shorter than the paced AV interval by ~30 ms.

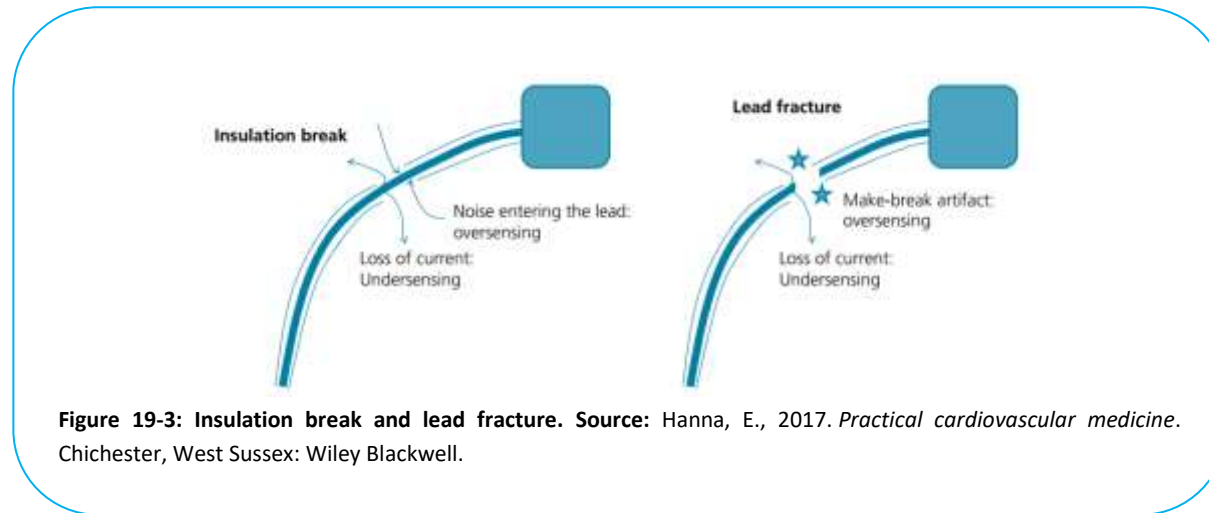
Complications:

▪ Implant related complications:

(1) Even if the lower rate interval is 1 second, the pacemaker may not initiate pacing until a 1.5 second pause occurs. In other words, the pacemaker may not start pacing until the ventricular rate falls to 40 bpm, after which it will start pacing at 60 bpm. This is the hysteresis function of a pacemaker. Hysteresis is a programmable feature that allows the pacemaker to begin ventricular pacing only if the spontaneous rate falls below a set rate (e.g 40 bpm); then pacing continues at the programmed base rate (e.g 60 bpm) unless intrinsic ventricular activity is sensed. It is done to reduce the burden of ventricular pacing.

- Complications related to subclavian puncture: pneumothorax, hemopneumothorax, air embolism, brachial plexus injury.
 - Hematoma at the pulse generator site.
 - Lead perforation which may result in cardiac tamponade.
 - Vein thrombosis of subclavian vein or SVC.
 - **Lead related complications:**
 - Lead dislodgement.
 - Exit block avoided by using steroid-eluting leads.
 - Lead fracture.
 - Loss of integrity of insulting material.

Lead fracture or insulation break is suspected from analysis of the lead impedance (a recent increase > 200 ohms in case of fracture or decrease > 200 ohms in case of insulation break). Lead or insulation breaks may be intermittent, and may be associated with a normal impedance, sensing, and capture at the time of interrogation. If an intermittent break is suspected, review stored EGMs looking for oversensed false signals, or perform Holter monitoring if the EGMs are unrevealing (PM may not store EGMs as it does not recognize that there is a problem). Also, perform maneuvers: move the generator in its pocket, move the ipsilateral arm (up and behind the back), perform a pulling maneuver with the ipsilateral arm, and assess capture during deep inspiration and after cough. CXR should be performed, but it does not always detect a lead fracture.
 - **Diaphragmatic stimulation:** Diaphragmatic stimulation may occur when the atrial lead is laterally placed in the RA, which stimulates the right phrenic nerve. It may also occur with a coronary sinus lead that stimulates the left phrenic nerve (BiV PM). Left diaphragmatic stimulation may also be seen with the RV lead, but more so if it perforates into the LV. That is why perforation must be excluded whenever diaphragmatic pacing is observed.
- Diaphragmatic stimulation may occur late after device placement, in which case it is usually related to an insulation break with loss of current into the surrounding muscles (diaphragm, deltopectoral muscles). Deltopectoral muscle stimulation is due to the use of unipolar leads or to insulation break.



- **Pacemaker system infection:** which may appear as local inflammation or abscess in the pacemaker pocket, erosion of part of the pacing system with secondary infection or sepsis with positive blood culture.
- **Pacemaker malfunction (Troubleshooting):**
- **Failure to sense (undersensing):**

Ventricular undersensing is a situation in which the pacemaker does not see intrinsic QRS and thus does not get inhibited by it. This leads to overpacing, with pacing spikes occurring regularly, including early after intrinsic QRS complexes and unrelated to them.

Causes of undersensing:

- Lead damage: lead fracture, insulation break, or loose connection of the lead to the generator (loose set screw, mainly seen early after PM implantation).
- Inappropriate programming (low sensitivity).
- Electromagnetic interference.
- Battery depletion.

- Undersensing of a PVC is possible and is not considered abnormal, especially when the PVC occurs shortly after QRS, within the ventricular refractory period.
- Undersensing of atrial activity may be seen in AF, where many of the small-amplitude atrial waves are not sensed by the device. This is treated by increasing the atrial sensitivity if AF is paroxysmal, or reprogramming the PM to a VVI mode if AF is permanent.
- Undersensing may also be seen in atrial flutter, where every other P wave falls in the blanking portion of PVARP and is not sensed. This precludes mode switching and allows tracking of the sensed P waves (e.g., atrial rate of 280 bpm, every other P is sensed and tracked at a fast rate of 140bpm). It is treated by shortening the blanking period.

- **Oversensing:**

Ventricular oversensing is a situation in which the pacemaker senses electrical activity that is not QRS and considers it V, therefore inhibiting the ventricular output. It does not pace the ventricle when it should. This leads to underpacing.

Causes of oversensing:

- Lead fracture or insulation break creating false signals.
- Inappropriate programming.
- The ventricular lead senses from a distance the atrial spike and considers it a ventricular event (far-field crosstalk). This is reduced by creating a post-atrial ventricular blanking period.
- Oversensing of a tall T wave and considering it QRS.
- Oversensing of myopotentials (diaphragmatic contractions, especially with unipolar leads) and electrocautery interference.

- **Failure to capture:**

In this case, the pacer spike occurs appropriately but is not followed by any paced activity (a paced QRS is not seen).

Causes of failure to capture:

- Lead fracture or insulation break.
- Inappropriate programming.
- Battery depletion.

- An increase in capture threshold due to drugs (class Ic overdose), MI, hyperkalemia, hypoxia, acidosis.
- Atrial failure to capture may be due to unsuspected AF. Many of the fibrillatory waves are unseen/undersensed by the PM, which leads to undersensing and pacing over AF without capture.
- Failure to capture may also occur in case of undersensing a premature complex, with subsequent pacing very close to it, in the refractory phase. The latter case may occur normally (functional non-capture).
- **Output failure:** Absence of a pacemaker spike (or spikes) when there should be one. This is caused by oversensing, failure to capture with small overlooked pacer spikes, or total battery failure.
Differentiate by magnet application, which solves oversensing but not the other two issues.

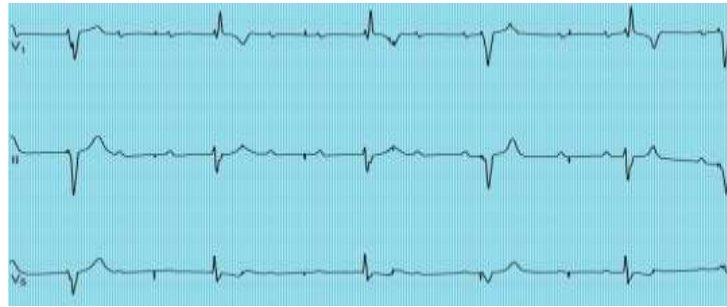


Figure 19-4: Undersensing (Failure to sense and failure to capture). This ECG shows an underlying sinus rhythm (rate 88 bpm) with complete heart block and a ventricular escape rhythm (rate of 29 bpm). There is a ventricular paced rhythm with intermittent failure to sense (undersensing). Undersensing is evident from the premature ventricular pacing stimulus outputs that are superimposed on the T waves of the first, second, and fifth QRS complexes (best seen in lead II). **Source:** Olshansky, Brian, et al. *Arrhythmia Essentials*. Elsevier, 2017.

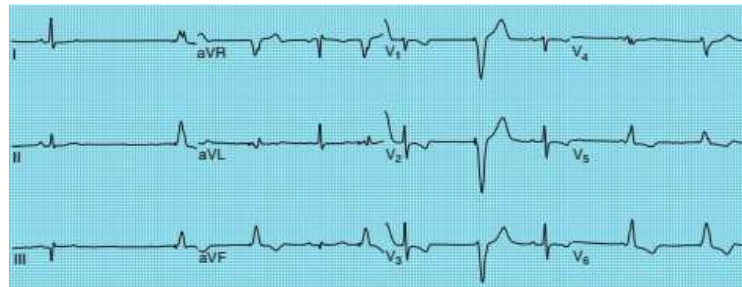


Figure 19-5: Oversensing (and undersensing). The 12-lead ECG shows an intrinsic marked sinus bradycardia with an irregular rhythm composed of native and ventricular paced complexes. The VV interval of the pacemaker, evident from the interval between the first and second ventricular pacing stimulus outputs (preceding the second and third QRS complexes), represents the key timing interval of the pacemaker. The pause between the first and second QRS complexes exceeds the VV interval, indicating oversensing of electrical activity with subsequent inhibition of pacemaker output, resulting in an inappropriate pause in rhythm. **Source:** Olshansky, Brian, et al. *Arrhythmia Essentials*. Elsevier, 2017.

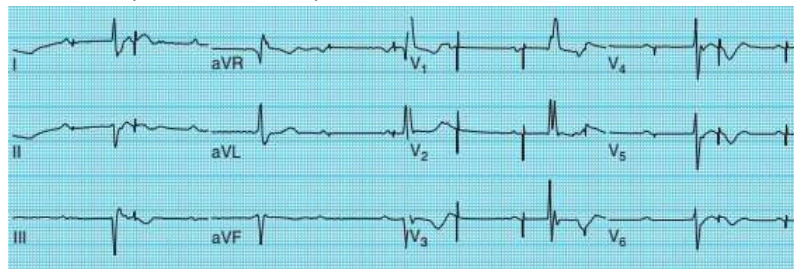


Figure 19-6: Failure to capture (ventricle). The 12-lead ECG shows an underlying sinus rhythm with complete heart block and a fascicular escape rhythm (right bundle branch block and left anterior fascicle block patterns) at a rate of about 29 bpm. A VVI mode of function is present, evident from ventricular stimulus outputs that do not regularly follow sinus P waves. There is clear failure to capture with absence of paced QRS complexes. **Source:** Olshansky, Brian, et al. *Arrhythmia Essentials*. Elsevier, 2017.

- **Specific Pacemaker abnormalities:**

- **Pacemaker syndrome:**

- Pacemaker syndrome is most commonly seen in the setting of a single chamber device with ventricular sensing and pacing lead. Since there is no atrial sensing lead to guide the ventricle, the ventricle contracts at the programmed rate regardless of the timing of atrial contraction. This leads to loss of AV synchrony which leads to back pressure in venous circulation systems that causes congestion (peripheral and pulmonary) as well as loss of atrial contribution leading to decreased cardiac output. VA conduction, which is usually a ventricular beat finding its way upwards to the atria also leads to a mistimed atrial contraction and produces similar effects.
- Physical examination reveals cannon "A" wave.
- The definitive treatment is conversion to dual chamber pacing.

- **Pacemaker-mediated tachycardia (PMT):**

- Also known as endless-loop tachycardia **or** pacemaker circus movement tachycardia.
- PMT is a complication of DDD pacing.
- PMT may be:
 - Rapid tracking of atrial fibrillation or flutter.
 - Rapid ventricular triggering from electromagnetic interference.
 - Endless-loop tachycardia in which VA conduction results in retrograde P waves being sensed as native atrial activity with subsequent ventricular pacing. The paced ventricular complex results in further retrograde conduction with retrograde p wave generation thus forming a continuous cycle. This results in a paced tachycardia with the maximum rate limited by the pacemaker programming. In the acute situation, placing a magnet over the pulse generator eliminating all sensing will terminate the rhythm. In the long term, the problem can be corrected by Lengthening postventricular atrial refractory period (PVARP) beyond retrograde P.

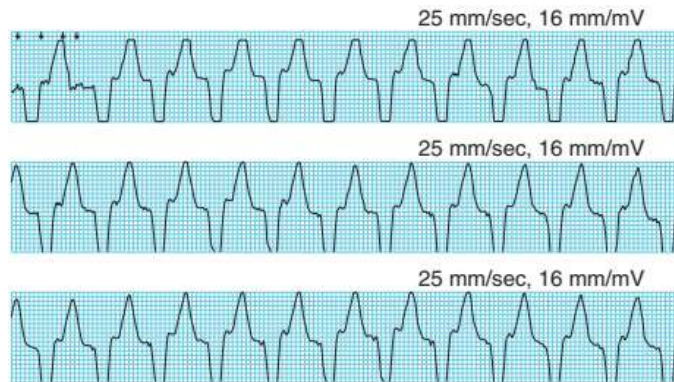


Figure 19-7: Pacemaker-mediated tachycardia. This lead II rhythm strip shows a rapid paced ventricular rhythm that represents pacemaker-mediated tachycardia (PMT). The characteristics of PMT are a rapid paced ventricular rhythm (usually near the programmed upper rate limit of the pacemaker) in which retrograde atrial activity (seen here in the down-sloping segment of the T waves of the ventricular paced beats) originating from ventricular paced beats is then sensed by the pacemaker, triggering a subsequent ventricular paced activation, the rhythm then becoming sustained. **Source:** Olshansky, Brian, et al. Arrhythmia Essentials. Elsevier, 2017.

- **Crosstalk:**

- This condition develops when an electrical event in one chamber is sensed in the other chamber and inappropriate inhibition of pacing occurs in the second chamber.
- To prevent the occurrence of crosstalk, two approaches have been incorporated in the pacemaker:
 - The ventricular blanking period at the time of the atrial impulse stimulus.
 - Safety pacing in which sensing any event during the early portion of the blanking period is followed by a committed early ventricular stimulus.
- **Twiddler's syndrome:** The pacemaker is turned (unintentionally) upside down within the pacemaker pocket. The leads may become twisted resulting in excessive traction on the leads and withdrawal from the heart. Can result in diaphragmatic or brachial plexus pacing (e.g. arm twitching) depending on extent of lead migration.

- **Fusion and pseudofusion:**

A pacemaker spike may be seen within a QRS that is intrinsically conducted through the AV node, or just before or after it. A pacer spike may also be seen just before, just after, or within a PVC.

This does not imply undersensing, as it takes time for the V channel to sense the intrinsic V activity. Even a pacing spike falling as far as the T wave may not mean undersensing.

A ventricular pacing spike falling just before the intrinsic complex may lead to a fusion beat, i.e., fusion between the pacing complex and the intrinsic complex. A ventricular pacing spike falling too close to the intrinsic complex may not lead to any conduction of pacer activity, a phenomenon called **pseudofusion**.

In this case, the lack of capture is called “*functional non-capture*”.

On the other hand, in a patient receiving both atrial and ventricular pacing, a PVC may fall over the atrial spike. The ventricular activity will be perceived as a ventricular activity occurring within the early period after atrial pacing and will trigger ventricular safety pacing. Thus, in addition to the A pacing spike, a V pacing spike is seen within the QRS or ST–T at a very short AV delay. The ventricular safety pacing should not be perceived as undersensing.

A PVC that falls too close to the intrinsic or paced ventricular complex, within the ventricular refractory period, may not be sensed and thus may not reset the atrial escape interval.

N.B: Differential diagnosis of a tachycardia occurring in a patient who has a DDD PM:

1. PMT, where the pacemaker tracks retrograde P waves.
2. Atrial arrhythmia is getting tracked by the pacemaker for one of the following reasons:
 - The atrial rate is slower than the mode-switch rate.
 - The arrhythmia is atrial flutter or AF with sensing of many, but not all, of the atrial waves; this alternate sensing prevents sensing the high rate and mode switching.
 - AF waves and some atrial tachycardia waves have a small amplitude and may, consequently, fall below the programmed atrial sensitivity wall; therefore, many of them are not sensed by the device and do not trigger a mode switch.

Differentiate from PMT by pacemaker interrogation and by placing a magnet. The P waves persist in the case of atrial arrhythmia, whereas the rhythm goes back to sinus in the case of PMT.

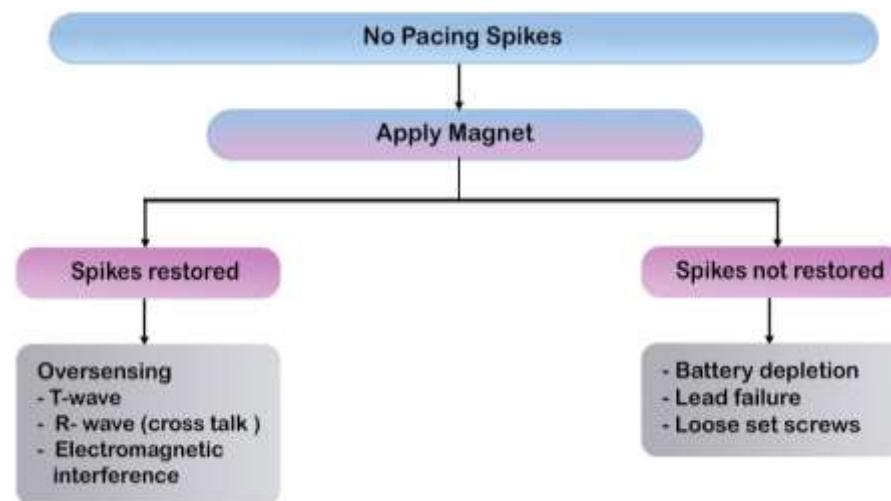
The inappropriate P-wave tracking is treated by reducing the rate at which mode switch occurs, by increasing atrial sensitivity, or by reducing the PVAB so that alternate atrial waves do not fall in the blanking period.

3. Oversensing myopotentials and tracking them.

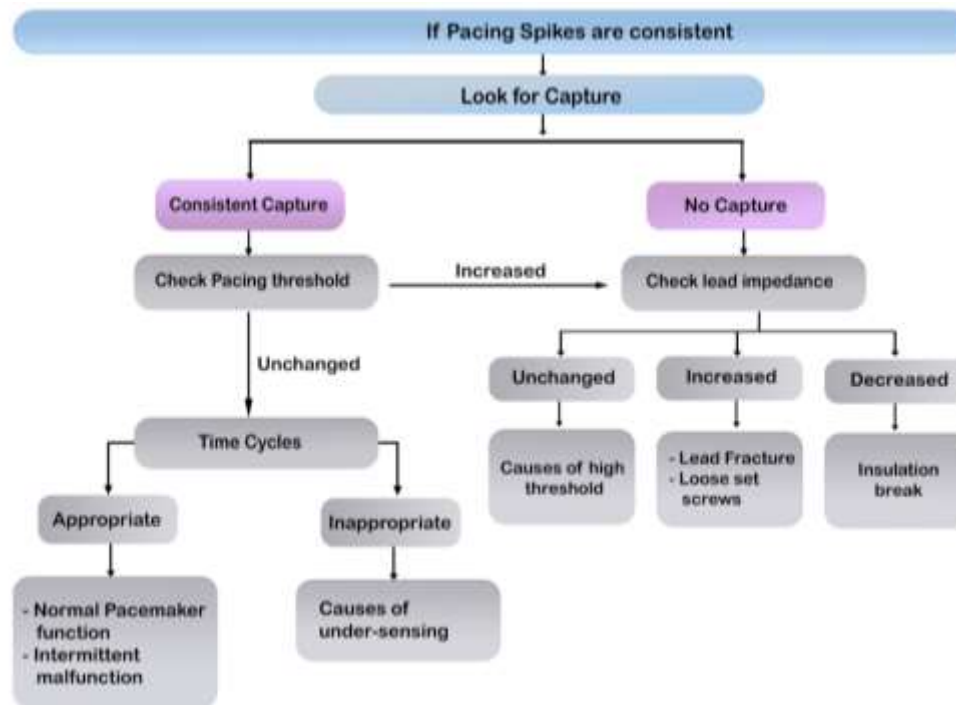
4. Any VT or SVT that is being spontaneously conducted, independently of the pacemaker. In contrast to the above three diagnoses, the ventricular activity is intrinsic rather than paced (no V pacing spike).

Assessment of pacemaker malfunction:

▪ If pacing spikes are absent:



▪ If pacing spikes are present:



Alternative pacing strategies and sites:

- **Septal pacing:** True RV pacing is not easily obtained and ascertained, and neither beneficial nor harmful effects of RVS pacing compared with RVA pacing have been shown on relevant clinical endpoints. Current evidence does not systemically recommend either RVS or RVA pacing for all patients.
- **His bundle pacing:** HBP was first reported in humans in 2000. Unlike the RV apex, pacing the proximal RV septum at the His level results in physiological, simultaneous activation of both ventricles along both bundles. His bundle pacing has been useful in 2 settings:

- In patients who require frequent ventricular pacing, whether EF is low or normal, His pacing prevents dyssynchrony and HF events.
- In patients with HF and LBBB, His pacing may be an alternative to CRT. The blocked left bundle is downstream from the His bundle, hence His pacing may still result in LBBB. Yet, increased-voltage His pacing often penetrates the left bundle beyond the block and corrects LBBB; His pacing narrows QRS in up to 75% of LBBB patients, and possibly improves EF and outcomes as much as CRT.

RV backup lead should be considered if: **(i)** the implanter is inexperienced, or **(ii)** if there are high capture thresholds or sensing issues in pacemaker-dependent patients, **(iii)** in those scheduled for AVN ablation (where there is risk of compromising HBP), or **(iv)** patients with high degree or infranodal block.

Table 19-4: Advantages and disadvantages of a ‘backup’ ventricular lead with His bundle pacing:

Advantages

- *Increased safety (in case of loss of capture of the HBP lead)*
- *Can be used for sensing (lower risk of ventricular undersensing, no risk of His or atrial oversensing)*
- *Programming of pacing output with lower safety margins*
- *May serve to narrow the QRS with fusion pacing in the case of selective-HBP with uncorrected RBBB*

Disadvantages

- *Higher cost*
- *More transvenous hardware*
- *Risk associated with the additional lead (e.g. ventricular perforation)*
- *More complex programming*
- *“Off-label” use (current regulatory approval and MRI-conditionality for HBP is only granted for His leads connected to the RV port)*

| Table 19-5: ESC Recommendations for using His bundle pacing: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>In patients treated with HBP, device programming tailored to specific requirements of HBP is recommended.</i> | I | C |
| <i>In CRT candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead.</i> | IIa | B |
| <i>In patients treated with HBP, implantation of an RV lead used as 'backup' for pacing should be considered in specific situations (e.g. pacemaker dependency, high-grade AVB, infranodal block, high pacing threshold, planned AVJ ablation) or for sensing in the case of issues with detection (e.g. risk of ventricular undersensing or oversensing of atrial/His potentials).</i> | IIa | C |
| <i>HBP with a ventricular backup lead may be considered in patients in whom a 'pace-and-ablate' strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when the intrinsic QRS is narrow.</i> | IIb | C |
| <i>HBP may be considered as an alternative to RV pacing in patients with AVB and LVEF > 40%, who are anticipated to have > 20% ventricular pacing.</i> | IIb | C |

- **Left bundle branch area pacing:**

With left bundle branch area pacing, the lead is implanted slightly distal to the His bundle and is screwed deep in the LV septum, ideally to capture the left bundle branch. Advantages of this technique are that electrical parameters are usually excellent, it may be successful in blocks that are too distal to be treated with HBP, and it also facilitates AVJ ablation, which may be challenging with HBP. However, although the technique is very promising, data on this modality are still scarce, and there is concern regarding long-term lead performance and feasibility of lead extraction.

- **Leadless pacing:**

Leadless pacemakers have been developed to address limitations typically related to pulse generator pocket and transvenous leads of conventional pacemaker systems. Indications for leadless pacemakers include: obstruction of the venous route used for standard pacemaker implantation (e.g. bilateral venous thoracic outlet syndrome or chronic obstruction of the superior vena cava), pocket issues (e.g. in the case of cachexia or dementia), or particularly increased infection risk [e.g. in the case of dialysis or previous cardiovascular implantable electronic device (CIED) infection]. There are currently no data from RCTs documenting the long-term safety and efficacy of leadless vs. standard transvenous pacemakers, and therefore the indication for a leadless pacemaker should be considered on a case by case basis.

| Table 19-6: ESC Recommendations for using leadless pacing: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Leadless pacemakers should be considered as an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on hemodialysis. | Ila | B |
| Leadless pacemakers may be considered as an alternative to standard single-lead ventricular pacing, taking into consideration life expectancy and using shared decision-making. | IIb | C |

Device follow-up:

The patient and the device should be treated as a single entity, with programming tailored to meet the patient’s needs. Remote device management is recommended to reduce the number of in-office follow-ups in patients with pacemakers who have difficulties to attend in-office visits (e.g. due to reduced mobility or other commitments, or according to patient preference).

| Table 19-7: Frequency of follow-up for routine pacemaker and CRT: | | |
|---|----------------|--------------------|
| | In-office only | In-office + remote |

| | | |
|--------------------------------|--|---|
| All devices | <i>Within 72 h and 2-12 weeks after implantation</i> | |
| CRT-P or HBP | <i>Every 6 months</i> | <i>Remote every 6 months and In-office every 12 months</i> |
| Single/dual chamber | <i>Every 12 months then every 3–6 months at signs of battery depletion</i> | <i>Remote every 6 months and In-office every 18 – 24 months</i> |

Management of pacemaker in special circumstances:

- **MRI in patients with implanted cardiac devices:**

MRI is a frequent requirement in patients with implanted pacemakers. It may cause adverse effects such as inappropriate device function due to device reset or sensing problems, interaction with the magnetic reed switch, induction of currents resulting in myocardial capture, heating at the lead tip with changes in sensing or capture thresholds, or lead perforation. In general, MRIs should always be performed in the context of a rigorously applied standardized institutional workflow, following the appropriate conditions of use (including programming).

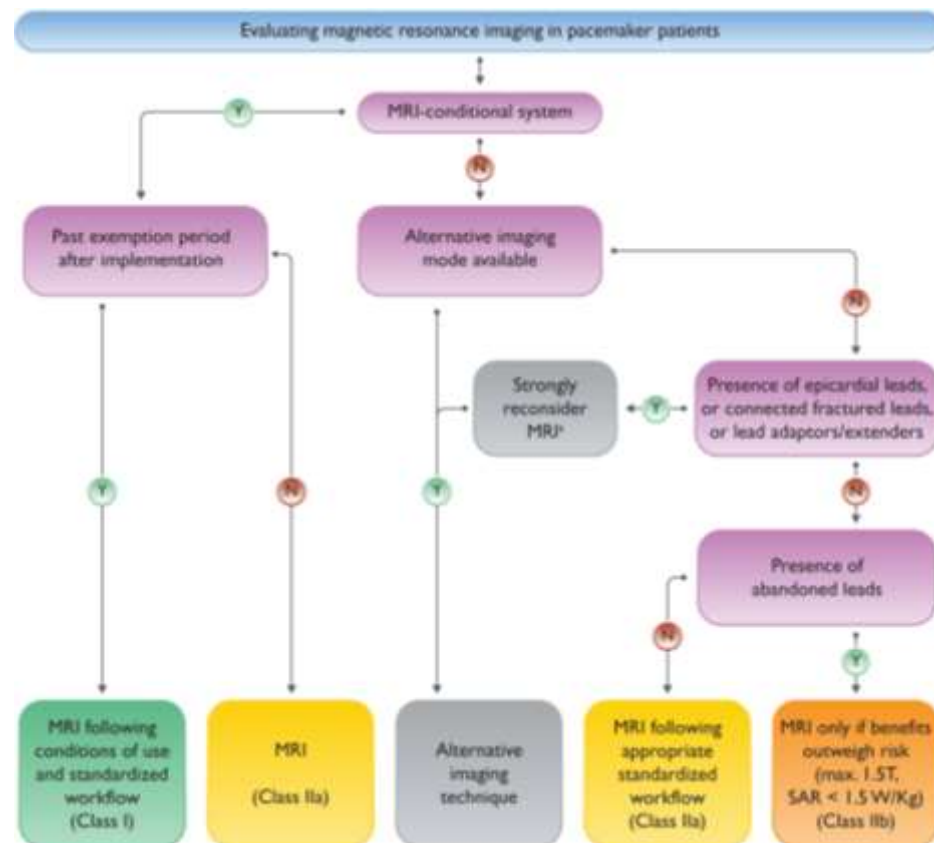


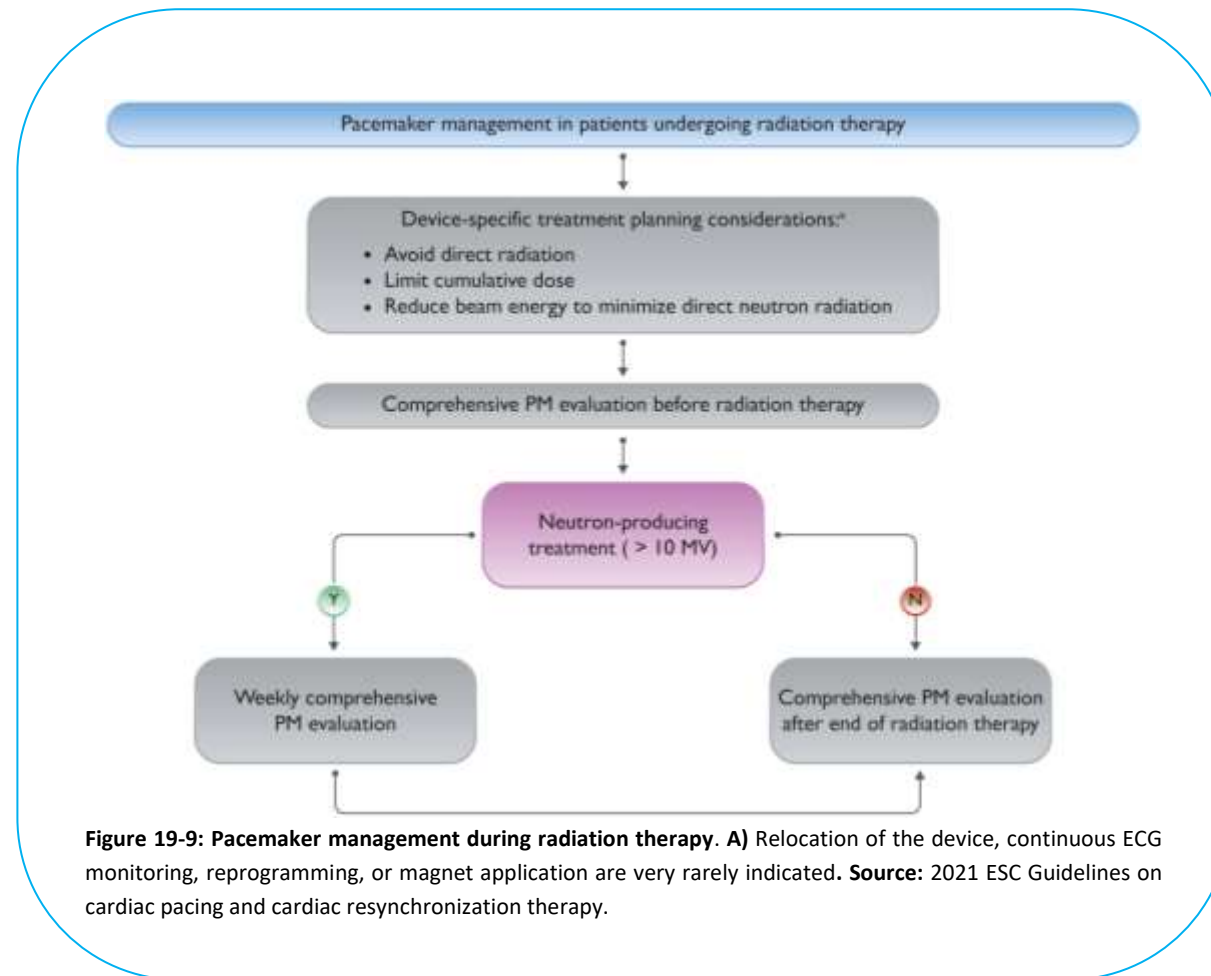
Figure 19-8: Flowchart for evaluating magnetic resonance imaging in pacemaker patients. SAR = specific absorption rate. **A)** Consider only if there is no imaging alternative and the result of the test is crucial for applying life-saving therapies for the patient. **Source:** 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.

Table 19-8: ESC Recommendations for performing MRI in pacemaker patients:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with MRI-conditional pacemaker systems (Combination of MRI-conditional generator and lead(s) from the same manufacturer), MRIs can be performed safely following the manufacturer's instructions.</i> | I | A |
| <i>In patients with non-MRI-conditional pacemaker systems, MRI should be considered if no alternative imaging mode is available and if no epicardial leads, abandoned or damaged leads, or lead adaptors/extendors are present.</i> | IIa | B |
| <i>MRI may be considered in pacemaker patients with abandoned transvenous leads if no alternative imaging modality is available.</i> | IIb | C |

▪ **Radiation therapy in pacemaker patients:**

- Radiotherapy uses high-energy ionizing radiation including X-rays, gamma rays, and charged particles, which might cause software and hardware errors in CIEDs, especially when photon radiation beam energy exceeds 6-10 MV, and the radiation dose to the device is high (> 2-10 Gy). During Radiation therapy, the pulse generator should be shielded from the ionizing radiation or moved to another site if necessary.



▪ **Applying a magnet over PM/ICD:**

- **On PM:** A magnet closes a reed switch in the generator and makes it convert to an asynchronous ventricular and/or dual pacing mode (VOO or DOO).

- **On ICD:** In contrast to a PM, the application of a magnet on an ICD does not affect the pacing mode or the sensing function (i.e., the DDD pacing function of an ICD keeps its DDD pacing function). It does not affect arrhythmia detection either. It only inhibits antitachycardia therapy and shock.
- **Peri-operative management of CIED:**
 - Electromagnetic interference (EMI) may induce:
 - Oversensing of electrical noise and inhibition of the PM output (more likely with unipolar leads). Oversensing may also result in ICD shock.
 - PM resets to a VOO mode, i.e., noise reversion mode.
 - Activation of rate-responsive sensors
 - Permanent damage to the pulse generator; or
 - Myocardial thermal injury at the lead tip, changing the sensing and pacing thresholds.
 - The most common source of EMI is electrocautery, although it is rare during bipolar electrocautery > 5 cm from the CIED and monopolar electrocautery below the umbilicus. Other sources of EMI include radiofrequency procedures, nerve stimulators, and other electronic devices.
 - To reduce the risk of EMI, unipolar electrocautery should be applied in short (< 5 s) pulses, with the skin patches away from the area of the device.
 - **Preoperatively, cardiac rhythm devices are managed as follows:**
 - **PM:** for pacemaker-dependent patients (no intrinsic activity), as evidenced by the baseline ECG and by the device interrogation, program the PM to VOO or DOO mode preoperatively (asynchronous uninhibited pacing) or place a magnet over it during delivery of diathermy pulses. CIEDs with a rate-responsive function using an active sensor may also require magnet application or disabling of this function to prevent inappropriate rapid pacing.
 - **ICD:** placing a magnet will inhibit the antitachycardia therapies, but will not lead to asynchronous pacing. Thus, if the patient has an ICD and is pacemaker-dependent, a magnet is not enough. The pacing function is programmed preoperatively to VOO or DOO, and the VT therapies are turned off.

- **Post-operative** CIED interrogation is recommended to assess sensing and capture thresholds, to ensure there is no “phantom” reprogramming of the device (noise reversion mode), and to turn the ICD therapies on.

N.B:

- Cellular phones are generally safe, but shouldn't be carried near the pacemaker site and avoid holding the telephone at the ipsilateral ear.
- For external cardioversion or defibrillation in a patient who has a PM/ICD, place the paddles in the anteroposterior position and at least 10 cm away from the pulse generator (right parasternal, left paraspinal). The anteroposterior position ensures that the shock vector is not coaxial with the leads. Interrogate the PM after the procedure.

Table 19-9: General recommendations on the perioperative management of patients with CIEDs:

- *Minimize the use of ipsilateral central lines, insert and remove pulmonary artery catheters under fluoroscopic guidance, and take every measure to prevent bacteremia if possible.*
- *Inform the patient on the potential risk of electromagnetic interference during the procedure, and take the measures aimed to prevent it in accordance with the patient's needs and preferences.*
- *Check the device before surgery if not done in the preceding 12 months or if battery longevity is unknown.*
- *Verify before surgery that the magnet mode is asynchronous pacing.*
- *The presence of pacemaker personnel in the building is necessary only in cases when device reprogramming is necessary or in procedures likely to cause strong electromagnetic interference.*
- *Magnets should be easily available in all operating rooms when procedures are done in cardiovascular implantable electronic device carriers.*
- *Monitor saturation waves if cautery impedes monitoring of the electrocardiogram.*
- *Check the device after surgery if malfunction is suspected or if the device has been exposed to significant electromagnetic interference.*

- **CIED and sports activity:**

Regular exercise is strongly recommended for prevention of cardiovascular disease.

In device patients, ***forceful contact sports*** (e.g., rugby, martial arts) should be avoided so as not to risk damage of device components or hematoma at the implantation site.

Cardiac resynchronization therapy (CRT)

Concept of CRT:

- CRT (also called biventricular pacemaker, BiV PM), is a pacemaker that typically has three leads: RA lead, RV lead, and LV epicardial lead placed via the coronary sinus. In a way, it is a DDD PM with an additional LV lead inserted percutaneously via the coronary sinus into the left lateral vein or surgically onto the lateral left ventricular wall.
- Approximately 20–30% of HF patients have QRS > 120 ms, mostly LBBB (70%); the remaining have RBBB or non-specific delay. Patients with LBBB, particularly > 150 ms, have mechanical dyssynchrony, wherein the RV and LV and various LV walls contract at different times. This dyssynchrony leads to:
 - **Impaired systolic function:** Depolarization and contraction of the LV free wall and LV base is significantly delayed compared to that of the RV, the interventricular septum, and the apex (inter- and intraventricular dyssynchrony). This leads to inefficient LV contraction, which increases LV systolic volume and reduces stroke volume.
 - **Impaired diastolic function:** LV further dilates with time as a result of reduced LV ejection. Moreover, the overall systolic time is ineffectively increased, which reduces the time provided for LV diastolic filling and thus increases LA pressure.
 - **Functional MR:** Dyssynchronous papillary muscle contraction and functional MR. If the posteromedial LV wall contracts before the anterolateral LV wall, the posterior leaflet is pushed up before the anterior leaflet, which precipitates or exaggerates leaflet non-coaptation; also, the posteromedial muscle relaxes while the anterolateral muscle is still contracting, which sustains leaflet non-coaptation.
- CRT improves survival, symptoms, and EF. It decreases LV systolic size (= reverse remodeling) and reduces functional MR (the two leaflets coapt at the same time when all segments contract simultaneously). CRT also improves diastolic function as it reduces systolic time, thus increasing the diastolic filling time. It leads to immediate improvement of symptoms, then reverse remodeling within months.

Indications of CRT:

| Table 19-10: ESC Recommendations for Indications of CRT: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| For HF purposes: | | |
| For symptomatic patients with HF in SR with LVEF $\leq 35\%$, | | |
| - CRT is recommended if QRS duration ≥ 150 ms, and LBBB QRS morphology | I | A |
| - CRT should be considered if QRS duration 130-149 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality. | IIa | A |
| For symptomatic patients with HF in SR with LVEF $\leq 35\%$, | | |
| - CRT should be considered if QRS duration ≥ 150 ms, and non-LBBB QRS morphology | IIa | B |
| - CRT may be considered if QRS duration 130-149 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity. | IIb | B |
| CRT should be considered for patients with HF and LVEF $\leq 35\%$ in NYHA class III or IV despite OMT if they are in AF and have intrinsic QRS ≥ 130 ms, provided a strategy to ensure biventricular capture is in place, in order to improve symptoms and reduce morbidity and mortality. | IIa | C |
| AVJ ablation should be added in the case of incomplete biventricular pacing (< 90-95%) due to conducted AF. | IIa | B |
| CRT is not indicated in patients with HF and QRS duration < 130 ms without an indication for RV pacing. | III | A |
| For AF purposes (If AV nodal ablation and pacing are performed to control the AF rate) ⁽¹⁾: | | |
| A) CRT is recommended in patients with HFrEF. | I | B |
| B) CRT rather than standard RV pacing should be considered in patients with HFmrEF. | IIa | C |

(1) AF ablation has been reported to improve LVEF and reduce the HF hospitalization rate in selected patients. In particular, when tachycardia-induced cardiomyopathy is highly probable. CRT should be considered in those patients with persistent AF and HFrEF when AF ablation cannot be performed or is declined by the patient.

| | | |
|---|------------|----------|
| C) RV pacing should be considered in patients with HFpEF. | Ila | B |
| D) CRT may be considered in patients with HFpEF. | Ilb | C |
| For Antibradycardic pacing: | | |
| <i>CRT (rather than RV pacing) is recommended for patients with HFrEF (< 40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.</i> | I | A |
| <i>Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF ≤ 35% despite OMT, and who have a significant ⁽¹⁾ proportion of RV pacing, should be considered for upgrade to CRT.</i> | Ila | B |

(1) A limit of 20% RV pacing for considering interventions for pacing-induced HF is supported by observational data. However, there are no data to support that any percentage of RV pacing can be considered as defining a true limit below which RV pacing is safe and beyond which RV pacing is harmful.

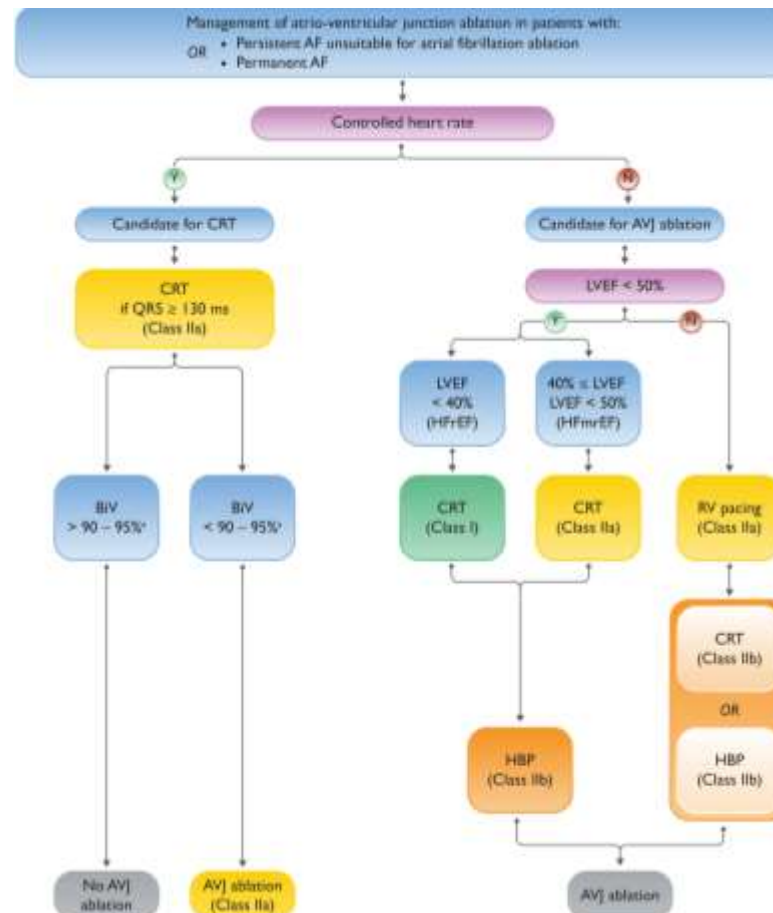


Figure 19-10: Indication for atrioventricular junction ablation in patients with symptomatic permanent or persistent AF unsuitable for atrial fibrillation ablation. A) Due to a rapid ventricular response. Source: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.

Optimization of CRT:

- To be beneficial, CRT has to track the atrial rate and pace both ventricles ~100% of the time. It cannot be in a standby mode. Observational studies report that when biventricular capture is < 98%, the prognosis of patients with CRT declines.
- **Optimization of AV delay:** CRT improves diastolic function by reducing systolic time, thus allowing more time for diastolic filling. However, an appropriate AV delay needs to be programmed to improve this diastolic filling.
 - First, AV delay should be shorter than the intrinsic PR interval to allow consistent biventricular pacing.
 - Second, the AV delay should not be too short; as very short PR makes A wave abut the ventricular systole (simultaneous AV contraction with interruption of A contribution to the diastolic filling).
 - Third, a long AV delay leads to fusion of A wave with E wave and induces diastolic MR.

The best AV delay is the one that allows clear E/A separation, with A wave ending at 40 ms after the QRS onset, corresponding to the exact onset of ventricular systole. This is achieved by setting the AV delay as long as possible while maintaining BiV pacing, then reducing it by 20 ms decrements until the optimal shape is achieved.
- In AF, the BiV PM is programmed in VVI mode (no A tracking). The AV conduction has to be aggressively slowed so that the intrinsic QRS rate is slow, and the BiV pacing would pace the ventricles at a rate faster than the spontaneous ventricular rate. CRT in patients with permanent AF and NYHA class III and IV with the same indications as for patients in SR, provided that AVJ ablation is added in those patients with incomplete (< 90-95%) biventricular capture due to AF. However, there are other causes for incomplete biventricular pacing such as frequent premature ventricular beats, which may need to be treated (with drugs or ablation) before considering AVJ ablation.

Response to CRT:

- A response to CRT therapy has been defined as an improvement of NYHA functional class or a reduction of LV end-systolic volume $\geq 15\%$, called reverse remodeling.

- Up to 25% of patients are super-responders, i.e., experience 15–20% improvement of LVEF (EF almost normalizes) in 6–12 months. A very wide LBBB, non-ischemic cardiomyopathy, female sex ⁽¹⁾, and LA volume < 40 ml/m² correlate with super-response. In those patients, dyssynchrony may be the direct cause of LV dysfunction.
- In responders, an immediate hemodynamic improvement is seen with CRT: improvement of LV filling, reduction of LA pressure, and improvement of LV dP/dt, MR, and cardiac output. Reverse remodeling, LVEF improvement, and further MR reduction are progressively seen over 3–12 months.
- 30% of patients do not respond to CRT (i.e. no reverse remodeling on echo), for the following reasons:
 - Treatment of patients with QRS 130-150 ms or RBBB ⁽²⁾, in whom electrical dyssynchrony does not necessarily imply mechanical dyssynchrony (This is the most common mechanism of non-response).
 - Large amount of scarred myocardium (e.g., patients with ischemic cardiomyopathy and scarring of > 50% of the myocardium are unlikely to benefit).
 - LV lead placement in a scarred region (pre-assessment with MRI may be useful).
 - LV lead positioning outside the area of latest activation on echocardiography.
 - LV lead positioned in the anterior or apical position rather than the lateral position. Lead position should be analyzed in a short-axis plane (anterior vs. posterolateral) and in a longitudinal plane (basal vs. apical). In most patients, the posterolateral basal wall is the site of latest activation.
 - Lack of appropriate AV optimization (seen in 10% of CRT patients).

N.B:

-
- (1)** A possible explanation for the greater benefit of CRT in women has been attributed to sex difference in LV size, as sex-specific differences in response disappear when QRS duration is normalized to LV end-diastolic volume.
- (2)** Patients with RBBB do not benefit from CRT unless they show a so-called **masked LBBB**. RBBB in patients with HF actually means generalized conduction and electromechanical delay rather than discrete right bundle delay. On ECG, masked LBBB is characterized by a broad, slurred, sometimes notched R wave on leads I and aVL, together with a leftward axis deviation.

- The QRS of a BiV-initiated complex is typically narrower than the RV pacemaker-initiated complex and the baseline non-paced QRS, even though the QRS often remains wide. Several studies have shown that a reduction in QRS width after CRT implantation is associated with a positive response to CRT. On average, QRS shortens by 20-40 ms with CRT. This QRS shortening is mostly seen in patients with a baseline QRS > 150 ms.
- After CRT implantation, a review of diuretic therapy is advised as a reduction in dose or its discontinuation may be required. In addition, CRT implantation may afford an opportunity to optimize MT for HFrEF.

Role of imaging in the assessment of efficacy of CRT:

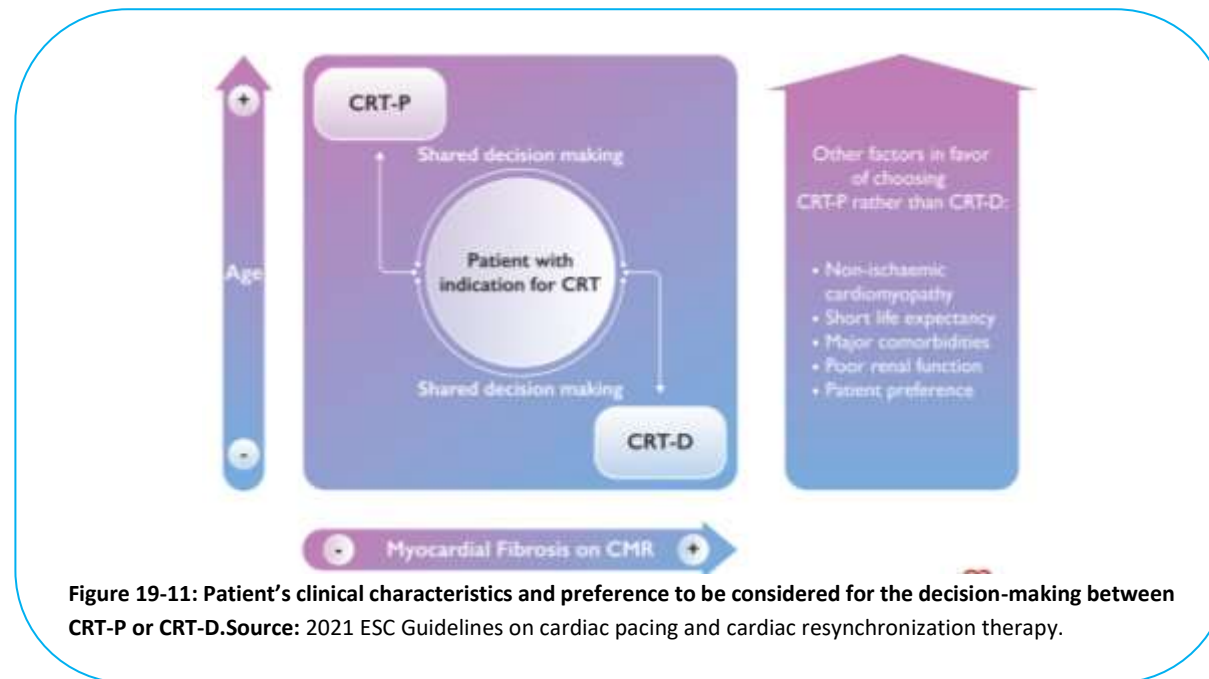
1. **Selection of patients for CRT:** Based on imaging, selection is limited only to the measurement of LVEF.
2. **Prediction of response to CRT:** Assessment of extent of myocardial scar, presence of mitral regurgitation, evaluation of electromechanical LV dyssynchrony or RV systolic function is important in identifying potential non-responders that may need additional treatment (e.g mitral valve intervention).
Echo parameters of dyssynchrony have not been shown to correlate with CRT response in patients with QRS > 130 ms (PROSPECT trial). However, these parameters may be beneficial in patients with QRS of 130-150 ms who are likely to respond to CRT (CARE-HF). To derive a benefit close to QRS > 150 ms, patients with QRS 130-150 ms required the fulfillment of two out of the following three criteria:
 - Aortic pre-ejection delay of > 140 ms: this is the delay between the onset of QRS and the onset of aortic flow (on the three- or five- chamber view).
 - Interventricular delay of > 40 ms: this is the difference between the left and right pre-ejection delay.
 - Septal-to-posterior wall motion delay > 130 ms (on M-mode of parasternal views).
3. **Guidance of LV lead implantation:** Myocardial tissue Doppler or tissue speckle-tracking may be used in the short-axis and apical views to see the site of latest activation. The site of latest activation that is not akinetic or scarred may be targeted for appropriate lead positioning. Randomized trials have not demonstrated that the guidance of LV lead implantation based on imaging (assessing myocardial scar or site of latest activation) is superior to standard practice (coronary sinus venography).

N.B: Evaluation of dyssynchrony is not helpful for QRS < 130 ms. Around 30% of HF patients with QRS < 130 ms have dyssynchrony on echo; however, CRT is not beneficial in them (RethinQ and EchoCRT trials).

Benefit of adding ICD in patients with indications for CRT:

There are no RCTs comparing CRT-P to CRT-D. While it is clear that CRT per se reduces mortality, most recent RCTs used CRT-D rather than CRT-P, especially those performed in patients NYHA II. Moreover, several observational studies did demonstrate a survival advantage of CRT-D over CRT-P, especially in patients with ischemic cardiomyopathy.

| Table 19-11: ESC Recommendations for adding a defibrillator with CRT: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>In patients who are candidates for an ICD and who have CRT indication, implantation of a CRT-D is recommended.</i> | I | A |
| <i>In patients who are candidates for CRT, implantation of a CRT-D should be considered after individual risk assessment and using shared decision-making.</i> | IIa | B |



Implantable cardioverter defibrillator (ICD)

Indications of ICD implantation:

- **Secondary prevention:** The use of ICD for secondary prevention of SCD demonstrated a 28% mortality reduction.
- **Primary Prevention:**

Table 19-12: Recommendations on primary preventive ICD therapy:

| Indication: | ESC class | ACC class |
|--|-----------|-----------|
| Coronary artery disease: | | |
| LVEF \leq 35% + NYHA functional class II-III | I | I |
| LVEF \leq 35% (ESC) / \leq 30% (AHA) + NYHA functional class I | IIa | I |

| | | |
|---|-----|-----|
| LVEF \leq 40% + NSVT + inducible monomorphic VT | Ila | I |
| LVEF \leq 40% + unexplained syncope + inducible monomorphic VT | Ila | I |
| NYHA functional class IV candidates for advanced HF therapy: | | |
| - Heart transplant | Ila | Ila |
| - LVAD | - | Ila |
| Nonischemic cardiomyopathy: | | |
| LVEF \leq 35% + NYHA functional class II-III | Ila | I |
| LVEF \leq 35% + NYHA functional class I | - | Ilb |
| Dilated cardiomyopathy: | | |
| Pathogenic mutation in LMNA gene: | | |
| - + \geq 2 risk factors (Male sex, NSVT, LVEF < 45%, nonmissense mutation) | | |
| - Estimated 5-y risk of VA \geq 10% + NSVT or AV conduction delay or LVEF < 50%. | | |
| LVEF > 35% and \geq 2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in PLN, FLNC, and RBM20 genes) | - | Ila |
| | Ila | - |
| LVEF > 35% and \geq 2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in PLN, FLNC, and RBM20 genes) | Ila | - |
| Arrhythmogenic right ventricular cardiomyopathy: | | |
| Arrhythmic syncope | Ila | Ila |
| Moderate RV (< 40%) or LV (< 45%) dysfunction + NSVT or inducible monomorphic VT | Ila | - |
| Significant RV dysfunction with LVEF \leq 35% | - | I |
| Significant RV dysfunction with RVEF \leq 35% | Ila | I |
| Hypertrophic cardiomyopathy: | | |
| Maximum left ventricular wall thickness \geq 30 mm | - | Ila |

| | | |
|---|------------|------------|
| SCD in first-degree relative presumably due to HCM | - | IIa |
| Unexplained syncope | - | IIa |
| NSVT or abnormal blood pressure response during exercise + additional SCD risk modifiers or high-risk features | - | IIa |
| NSVT or abnormal blood pressure response during exercise without additional SCD risk modifiers or high-risk features | - | IIb |
| Estimated 5-y risk of sudden death based on the HCM Risk-SCD Calculator $\geq 6\%$ | IIa | - |
| Estimated 5-y risk of sudden death based on HCM Risk-SCD Calculator (≥ 4 to $<6\%$) + Significant LGE at CMR <u>or</u> LVEF $< 50\%$ <u>or</u> Abnormal blood pressure during exercise test <u>or</u> LV apical aneurysm <u>or</u> Presence of sarcomeric pathogenic mutation. | IIa | - |
| Estimated 5-y risk of sudden death based on the HCM Risk-SCD Calculator ≥ 4 to $<6\%$ | IIb | - |
| Estimated 5-y risk of sudden death based on the HCM Risk-SCD Calculator $< 4\%$ + Significant LGE at CMR <u>or</u> LVEF $< 50\%$ <u>or</u> LV apical aneurysm | IIb | - |
| Congenital long QT syndrome: | | |
| Symptomatic high-risk patients + ineffectiveness or intolerance of beta-blocker therapy ⁽¹⁾ (high risk: QTc > 500 ms, genotypes LQTS2 and LQTS3, LQTS2 females, age <40 y, onset of symptoms < 10 y, recurrent syncope) | - | I |
| Unexplained syncope during beta-blocker and genotype-specific therapy | I | - |
| Symptomatic patients + intolerance or contraindication of beta-blockers and genotype-specific therapy | IIa | - |
| Asymptomatic patients with QTc > 500 ms during beta-blocker treatment | - | IIb |
| Asymptomatic patients with high risk profile according to 1-2-3- LQTS-Risk calculator | IIb | - |

(1) ESC guideline: preferably nonselective beta-blocker (nadolol or propranolol).

| | | |
|--|-----|---|
| Catecholaminergic polymorphic ventricular tachycardia: | | |
| Syncope during beta-blocker treatment | - | I |
| Syncope during combined beta-blocker and flecainide treatment | IIa | - |
| Brugada syndrome: | | |
| Spontaneous type 1 Brugada ECG + recent history of syncope presumed due to ventricular arrhythmia. | IIa | I |
| Asymptomatic patients with inducible ventricular fibrillation | IIb | - |

Technical aspects of ICD implantation:

- An ICD has one (V) or two (A + V) leads. In addition to antitachycardia capacity provided by the special RV lead, it has single- or dual-chamber sensing and pacing capacities (VVI or DDD).
- The V lead has one (RV) or two coils (RV + SVC) that allow the delivery of the shock energy. The vector of shock goes between the battery can and the coil; in patients with two coils, the vector may be modified to provide superior efficacy (e.g., can-to-RV, or can+SVC- to-RV).
- The ICD is best placed on the left side to allow the vector of shock to be orthogonal to the heart, fully traversing the myocardium.
- Complications of transvenous ICD: inappropriate therapies, lead fractures, and device-related infections.
- **Other Types of ICD:**
 - A subcutaneous ICD (S-ICD) has been introduced to address problems related to transvenous leads. S-ICD has no intravascular lead and therefore cannot deliver ATP.
 - The wearable cardioverter defibrillator (WCD) is an external defibrillator that has been shown to successfully detect and treat VT/VF. It is suitable for patients who are at risk but temporarily not candidates for ICD, for example, due to extraction of infected device and subsequent antibiotic treatment.

| Table 19-13: ESC Recommendations for ICD implantation: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>Implantation of ICD is only recommended in patients who have an expectation of good quality survival > 1 year.</i> | I | C |
| <i>It is not recommended to implant an ICD in patients with incessant VAs until the VA is controlled.</i> | III | C |
| <i>ICD implantation is recommended in patients with documented VF or hemodynamically not-tolerated VT in the absence of reversible causes.</i> | I | A |
| <i>In patients with VT/VF, an indication for ICD, and no contraindication for amiodarone, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons, or declined by the patient.</i> | IIb | C |
| <i>In patients with SMVT or SPVT/VF triggered by a PVC with similar morphology and an indication for ICD, catheter ablation may be considered when an ICD is not available, contraindicated for concurrent medical reasons, or declined by the patient.</i> | IIb | C |
| Subcutaneous defibrillator: | | |
| <i>Subcutaneous defibrillator should be considered as an alternative to transvenous defibrillator in patients with an indication for an ICD when pacing therapy for bradycardia, cardiac resynchronization, or ATP is not needed.</i> | IIa | B |
| Wearable cardioverter defibrillator: | | |
| <i>The WCD should be considered for adult patients with a secondary prevention ICD indication, who are temporarily not candidates for ICD implantation.</i> | IIa | C |
| <i>The WCD may be considered in the early phase after MI in selected patients.</i> | IIb | C |
| Adding CRT to ICD: | | |

When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from CRT-defibrillator.

I

C

Optimization of device programming:

Optimization of ICD programming is essential to minimize the burden of ICD therapy and to improve patient outcome.

- **Bradycardia mode:** The pacing function is a standby function that should only be initiated at low ventricular rates (e.g., 40 bpm) to prevent unnecessary RV pacing, thus reducing HF hospitalizations and all-cause mortality.
- A tachycardia detection programming strategy incorporating prolonged settings and high-rate thresholds (≥ 188 b.p.m. Advance III trial, ≥ 200 MADIT-RIT) reduces ICD therapies and all-cause mortality without increasing the risk of syncope.
- The sensing function is what detects VF/VT. Typically, a certain ventricular rate is considered VT, regardless of its true origin. Many ICDs are programmed into two detection zones: VT and VF. Those two zones are differentiated by their rate (e.g., VT zone encompasses any ventricular rate of 170–220; VF zone encompasses ventricular rates > 220).
- **SVT-VT discrimination algorithms:** ICD may have on the other hand, SVT-VT discrimination algorithms, particularly the dual-chamber ICD, wherein the atrial lead can see the atrial activity:
 - Irregularity of ventricular activity during tachycardia \rightarrow AF
 - Progressive onset \rightarrow sinus tachycardia
 - More atrial activity than ventricular activity \rightarrow SVT; more ventricular activity than atrial activity \rightarrow VT
 - No significant change in the morphology of the ventricular electrogram as compared to baseline \rightarrow SVT.

These discrimination algorithms are applied only for the VT zone. Any tachycardia in the VF zone is considered VF. Moreover, these discrimination algorithms *may* have a time out. For example, ICD may be programmed in such a way that if the tachycardia persists more than 5 minutes it is treated as VT regardless of the initial diagnosis.

- **ATP:** Typically, VT is initially treated with multiple cycles of antitachycardia pacing (ATP: overdrive ventricular pacing at a cycle length ~85% the tachycardia cycle length). Systematic use of ATP before shock delivery has been shown to reduce shock therapy without increase in arrhythmic syncope.
- If these fail, the ICD delivers a shock. If the tachycardia is fast enough to fall in the programmed VF zone, ICD immediately delivers a maximal shock.

N.B: ATP enters the VT reentry cycle and breaks it in many patients; however, if the excitable gap of the reentry is wide, ATP may entrain the reentry at a faster rate, and may trigger further reentries that lead to VF. In fact, the most important ICD primary prevention trial (SCD-HeFT) recommended against ATP therapy and used a single-chamber rather than dual-chamber ICD, with shock therapy for tachycardia > 187 bpm.

Differential Diagnosis of an ICD shock:

- **Appropriate shock for VT/VF:** clinically, the patient often feels palpitations, malaise, or dizziness before the shock occurs. In the case of sudden and repeated episodes of VT (VT storm), look for triggers: active ischemia, decompensated HF, electrolyte imbalance, TdP (long QT due to drugs). In a patient with chronic cardiomyopathy, sudden back-to-back episodes of VT/VF may not have any particular trigger.
Manage the triggers, and, if necessary, place the patient on amiodarone+ β -blocker, or sotalol.
- **Inappropriate shock for SVT:** the ICD considers any tachycardia above a certain programmed rate (e.g., 170 bpm) as VT and treats it as such, with antitachycardia overdrive pacing initially, then a shock if it persists. This may occur with AF, atrial flutter, AVNRT/AVRT, or sinus tachycardia during strenuous activity (clue to the latter: shock during strenuous activity). The ICD may use SVT–VT discrimination algorithms to withhold on treating SVT.
- **Inappropriate shock due to oversensing:**
 - Oversensing T wave.
 - Far-field sensing of the atrial spike.

- Myopotentials: oversensing myopotentials may be reproduced by asking the patient to exercise (move arms across shoulder, compress hands together).
- Electromagnetic interference (e.g., welding).
- Lead fracture or insulation break may also lead to oversensing of false signals (shock during repetitive shoulder movements).
Hints: lead impedance changes with time, sometimes intermittently; interrogation shows extra spikes on the ventricular channel, particularly when performed during deep inspiration or during arm or can movement. Also, the situation in which the shock occurs helps with the diagnosis of lead issues, myopotentials, and electromagnetic interference.

Management of ICD shock:

- An ED visit is usually required after an ICD shock, especially if the clinical status changes or multiple shocks occur.
- Interrogate the device to distinguish between appropriate and inappropriate shocks. Look for triggers, assess HF status, and perform ECG and chest X-ray. In the absence of a reversible cause, institute an antiarrhythmic agent. Because amiodarone may increase the defibrillation threshold and VF detection threshold, the ICD defibrillation threshold may need to be retested after amiodarone institution. Also, amiodarone may slow VT below the detection zone; thus, a new, lower-limit VT monitoring zone should be instituted to see if this phenomenon happens.
- In case of SVT, make sure SVT–VT discrimination algorithms are on (only applies to VT zone, not VF zone) and consider using a higher rate threshold for the institution of VT therapies. SVT may be treated with antiarrhythmic drugs.

Concomitant treatment to avoid inappropriate ICD therapy

- Apart from optimization of device programming, pharmacological and/or invasive management may prevent inappropriate ICD therapy. Beta-blockers (carvedilol superior to metoprolol in MADIT-CRT) should be uptitrated in HF patients to reduce the risk of inappropriate therapy.
- In patients with inappropriate therapies due to recurrent SVT, catheter ablation should be first-line treatment, given its high success and low complication rate.

- In case of AF-related inappropriate therapies, individualized treatment strategy (rate vs. rhythm) dependent on patient characteristics is suggested. Rhythm control strategy improved patient outcome in the early AF (EAST-AFNET 4 trial).

Strategies to reduce devices complications:

- Antibiotic prophylaxis, peri-procedural patient preparation, and appropriate surgical technique should be implemented to prevent device infections and formation of pocket hematoma.
- Cephalic or axillary vein access is preferred over the subclavian vein route to reduce the risk of pneumothorax and lead failure.
- Proper selection of ICD systems is important. Single-chamber ICDs are recommended in primary prevention patients without atrial or AV sequential pacing indications to reduce peri-procedural complications and generator replacements. This approach does not increase the risk of inappropriate shocks if optimal device programming is used.
- Routine use of single-coil defibrillator leads is favoured due to reduced risk of complications during lead removal without associated differences in shock efficacy. Use of dual-coil leads can be considered in clinical settings where a higher defibrillator threshold is suspected, e.g., HCM, right-sided implantations.

| Table 19-14: ESC Recommendations for ICD optimization to decrease inappropriate ICD shocks: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>Optimization of ICD programming is indicated to avoid inappropriate and unnecessary therapies and to reduce mortality.</i> | I | A |
| <i>In single- or dual-chamber ICD patients without bradycardia pacing indications, it is recommended to minimize ventricular pacing.</i> | I | A |
| <i>Programming of prolonged detection settings is indicated (duration criteria of at least 6-12 s or 30 intervals).</i> | I | A |
| <i>It is recommended to program the slowest tachycardia therapy zone limit ≥ 188 b.p.m. in primary prevention ICD patients.</i> | I | A |

| | | |
|--|-----|---|
| <i>In patients with SHD, programming of at least one ATP therapy is recommended in all tachyarrhythmias zones.</i> | I | A |
| <i>It is recommended to program algorithms for SVT vs. VT discrimination for tachycardias with rates up to 230 b.p.m.</i> | I | B |
| <i>It is recommended to activate lead failure alerts.</i> | I | B |
| <i>Remote monitoring is recommended to reduce the incidence of inappropriate shocks.</i> | I | B |
| <i>Programming of burst ATP as first attempt is recommended over ramp ATP (due to increased efficacy in first tachycardia termination)</i> | I | B |
| <i>For S-ICDs, a dual detection zone configuration is recommended with activation of discrimination algorithm in the lower conditional shock zone.</i> | I | B |
| <i>For routine ICD programming, activation of more than one tachycardia detection zone should be considered.</i> | IIa | B |
| <i>Catheter ablation is recommended for ICD patients with recurrent SVT resulting in inappropriate ICD therapies.</i> | I | C |
| <i>Pharmacological treatment or catheter ablation is recommended in patients with AF-related inappropriate ICD therapies despite optimal ICD programming.</i> | I | C |
| Prevention of ICD complications: | | |
| <i>Single-chamber ICD is recommended over dual-chamber ICD in primary prevention patients without current or expected indication for atrial or AV sequential pacing due to a lower risk of device-related complications.</i> | I | A |
| <i>The use of single-coil leads over dual-coil ICD leads should be considered due to lower complication rate during transvenous lead extraction.</i> | IIa | C |

N.B: ICD in Patients with LVAD:

VAs are common among left ventricular assist device (LVAD) carriers. VAs are usually well-tolerated, as LVADs maintain adequate cardiac output and prevent circulatory collapse. However, sustained untreated VAs may lead to circulatory collapse even in the presence of an LVAD, especially early after device implantation and in patients with higher pulmonary vascular resistance.

Observational studies in patients with previous-generation, pulsatile LVADs reported a longer survival with ICD. Recent registries enrolling continuous-flow LVAD carriers have questioned ICD mortality reduction. The lack of documented survival benefit among continuous-flow LVAD carriers, in conjunction with the likelihood of VA tolerance and the associated risks of ICD placement in these patients (risk of infection, device interaction), favours an individualized approach.

Important trials in cardiac devices:

| Table 19-15: Clinical trials in cardiac devices: | |
|--|--|
| Trial (date) | Summary |
| CRT: | |
| MIRACLE (2002) | <p>Aim: To compare the effect of CRT versus no CRT on the quality of life and functional capacity in patients with HF and ventricular dysynchrony.</p> <p>Study: 453 patients with moderate-to-severe symptoms of HF associated with an $EF \leq 35\%$ and a QRS interval ≥ 130 msec were randomly assigned to a CRT group or to a control group for six months, while conventional therapy for HF was maintained. CRT results in significant clinical improvement in patients who have moderate-to-severe HF and an intraventricular conduction delay.</p> |
| COMPANION (2004) | <p>Aim: To compare optimal pharmacological therapy with CRT, or CRT with defibrillator (CRT-D) in patients with advanced chronic heart failure.</p> <p>Study: 1520 patients who had advanced heart failure (NYHA III-IV) due to ischemic or non-ischemic cardiomyopathies and $QRS \geq 120$ msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy (diuretics, ACE-Is, beta-blockers, and spironolactone) alone or in combination with CRT therapy with either a pacemaker or a pacemaker–defibrillator. CRT decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality.</p> |
| CARE-HF (2005) | <p>Aim: To evaluate the addition of CRT to optimal pharmacological therapy in patients with advanced HF and cardiac dyssynchrony.</p> <p>Study: 813 patients with NYHA III-IV heart failure with $LVEF \leq 35\%$ and cardiac dyssynchrony who were receiving standard pharmacologic therapy were randomly assigned to receive medical therapy alone or with cardiac resynchronization. The primary end point was the time to death from any cause or an unplanned hospitalization for a MACE. CRT improves symptoms and the quality of life and reduces complications and the risk of death.</p> |

| | |
|-------------------------|---|
| MADIT-CRT (2009) | <p>Aim: <i>To determine whether CRT with biventricular pacing would reduce the risk of death or heart-failure events in patients with mild cardiac symptoms, a reduced ejection fraction, and a wide QRS complex.</i></p> <p>Study: <i>During a 4.5-year period, 1820 patients with ischemic or nonischemic cardiomyopathy, an EF \leq 30%, a QRS duration \geq 130 msec, and NYHA class I or II were randomly assigned in a 3:2 ratio to receive CRT-D or ICD alone. The primary end point was death from any cause or a nonfatal HF event. CRT combined with ICD decreased the risk of HF events in relatively asymptomatic patients with a low EF and wide QRS complex.</i></p> |
| RAFT (2010) | <p>Aim: <i>To evaluate whether adding CRT to an ICD and optimal medical therapy might reduce mortality and morbidity among such patients.</i></p> <p>Study: <i>1798 patients with NYHA class II or III, a LVEF \leq 30%, and an intrinsic QRS duration \geq 120 msec or a paced QRS duration \geq 200 msec to receive either an ICD alone or an ICD plus CRT. The primary outcome was death from any cause or HF hospitalization. The addition of CRT to an ICD reduced rates of death and HF hospitalization. This improvement was accompanied by more adverse events.</i></p> |
| Echo-CRT (2013) | <p>Aim: <i>to investigate the effect of CRT on morbidity and mortality among patients with symptomatic heart failure, a narrow QRS complex, and echocardiographic evidence of LV dyssynchrony.</i></p> <p>Study: <i>809 patients with NYHA class III or IV heart failure, a LVEF \leq 35%, a QRS duration \leq 130 msec, and echocardiographic evidence of LV dyssynchrony. All patients underwent device implantation and were randomly assigned to have CRT capability turned on or off. The primary efficacy outcome was the composite of death from any cause or first hospitalization for worsening heart failure. In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality.</i></p> |
| BLOCK HF (2013) | <p>Aim: <i>To evaluate whether biventricular pacing might reduce mortality, morbidity, and adverse LV remodeling in patients with AV block, but high percentages of RV apical pacing.</i></p> |

| | |
|------------------------|---|
| | <p>Study: 691 patients with AV block; NYHA class I:III heart failure; and LVEF \leq 50% received CRT or ICD were randomly assigned to standard RV pacing or biventricular pacing. Biventricular pacing was superior to conventional right ventricular pacing.</p> |
| REVERSE (2013) | <p>Aim: To evaluate CRT compared with optimal medical therapy among patients with NYHA class I-II HFrEF and ventricular dyssynchrony.</p> <p>Study: 610 patients with LV dysfunction and NYHA class I-II underwent CRT implant and were randomized to CRT <u>ON</u> <u>or</u> CRT OFF with optimal medical therapy. The use of CRT in patients with mildly symptomatic HF did not reduce the proportion of patients who clinically worsened at 12 months, but it did delay the time to first hospitalization for heart failure. There was no difference in mortality. This therapy resulted in significant reverse LV remodeling, which remained stable to 5 years.</p> |
| ICD: | |
| DEFINITE (2004) | <p>Aim: To evaluate whether standard medical therapy plus an ICD will be associated with improvements in survival compared with standard medical therapy alone in patients with nonischemic dilated cardiomyopathy, EF \leq 35%, and spontaneous PVCs or nonsustained VT.</p> <p>Study: 458 patients with nonischemic dilated cardiomyopathy, LVEF \leq 35%, and PVCs or nonsustained VT were randomly assigned to receive standard medical therapy, and to standard medical therapy plus a single-chamber ICD. ICD in addition to standard medical therapy significantly reduced the risk of sudden death from arrhythmia and was associated with a non-significant reduction in the risk of death from any cause.</p> |
| AMIOVIRT (2003) | <p>Aim: To compare total mortality during therapy with amiodarone or an ICD in patients with nonischemic dilated cardiomyopathy and NSVT.</p> <p>Study: 103 patients with dilated cardiomyopathy, LVEF \leq 35%, and asymptomatic NSVT were randomized to receive either amiodarone or an ICD. The primary end point was total mortality. Mortality and quality of life in patients with NIDCM and NSVT treated with amiodarone or an ICD are not statistically different. There is a trend towards a more beneficial cost profile and improved arrhythmia-free survival with amiodarone therapy.</p> |

| | |
|----------------------------|--|
| SCD-HeFT (2005) | <p>Aim: <i>To evaluate the hypothesis that amiodarone or a conservatively programmed shock-only, single-lead ICD would decrease the risk of death from any cause in a broad population of patients with mild-to-moderate heart failure.</i></p> <p>Study: <i>2521 patients with NYHA II-III CHF and LVEF \leq 35% were randomly assigned to conventional therapy for CHF plus placebo, conventional therapy plus amiodarone, or conventional therapy plus a conservatively programmed, shock-only, single-lead ICD. The primary end point was death from any cause. Amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23%.</i></p> |
| DANISH (2016) | <p>Aim: <i>To assess the efficacy of ICDs in patients with non-ischemic systolic heart failure on mortality</i></p> <p>Study: <i>556 patients with symptomatic non ischemic cardiomyopathy (LVEF \leq 35%) were assigned to receive an ICD, and to usual medical therapy. In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. Prophylactic ICD in patients with symptomatic systolic HF not caused by CAD was not associated with significantly lower rate of death from any cause than was usual clinical care.</i></p> |
| MADIT (1996) | <p>Aim: <i>To assess whether prophylactic therapy with an ICD, as compared to pharmacotherapy, would improve survival in patients with coronary disease at high risk for ventricular arrhythmia.</i></p> <p>Study: <i>196 patients in NYHA class I, II, or III with prior MI; a LVEF $<$ 35%; a documented episode of asymptomatic unsustained VT; and inducible, nonsuppressible VT on EP study were randomly assigned to receive an ICD or conventional medical therapy. Prophylactic ICD leads to improved survival as compared with conventional medical therapy.</i></p> |
| MUSTT (1996) | <p>Aim: <i>To determine the value of EP-guided antiarrhythmic therapy in coronary heart disease patients at increased risk for sudden death.</i></p> <p>Study: <i>2202 eligible patients with nonsustained VT, LVEF $<$ 40%, and coronary artery disease all had an EP study to determine whether they had inducible sustained VT. If they had inducible VT, they were randomized to either conservative treatment (with an ACE inhibitor and/or beta-blocker) or EP-guided treatment using the following drug sequence: (Round 1) propafenone or sotalol; (Round 2) Type IA agent and mexiletine or ICD or another</i></p> |

| | |
|---------------------------|---|
| | <i>round 1 agent; (Round 3) amiodarone, ICD, or another round 1 or 2 agent. No statistically significant difference in the frequency or duration of spontaneous nonsustained VT was seen between patients with and those without inducible sustained VT. Rates of spontaneous tachycardia were slightly slower in patients with inducible VT than in patients without inducible VT, but the difference was not clinically significant.</i> |
| MADIT-II (2002) | <p>Aim: <i>To evaluate the effect of ICD on survival in patients with reduced LV function after MI.</i></p> <p>Study: <i>1200 patients with a prior MI and a LVEF $\leq 30\%$ were randomly assigned in a 3:2 ratio to receive an ICD or conventional medical therapy. Death from any cause was the endpoint. Prophylactic implantation of ICD improves survival and should be considered as a recommended therapy.</i></p> |
| DINAMIT (2004) | <p>Aim: <i>To evaluate the effects of prophylactic ICD therapy in high-risk patients early after acute MI.</i></p> <p>Study: <i>674 patients with LVEF $\leq 35\%$ and impaired cardiac autonomic function (manifested as depressed heart-rate variability or an elevated average 24-hour heart rate on Holter monitoring) were randomly assigned to ICD therapy and no ICD therapy 6 to 40 days after MI. The primary outcome was mortality from any cause. Death from arrhythmia was a predefined secondary outcome. Prophylactic ICD therapy does not reduce overall mortality in high-risk patients who have recently had a MI. Although ICD therapy was associated with a reduction in the rate of death due to arrhythmia, that was offset by an increase in the rate of death from nonarrhythmic causes.</i></p> |
| IRIS (2009) | <p>Aim: <i>To evaluate ICD therapy in patients with low EF or other high-risk criteria early after acute MI.</i></p> <p>Study: <i>898 patients were enrolled 5 to 31 days after the event if they met certain clinical criteria: a reduced LVEF $\leq 40\%$ and a heart rate ≥ 90 bpm, nonsustained VT (≥ 150 bpm) during Holter monitoring, or both criteria. Those patients were randomly assigned to treatment with an ICD and to medical therapy alone. Prophylactic ICD therapy did not reduce overall mortality among patients with acute MI and clinical features that placed them at increased risk.</i></p> |
| EU-CERT-ICD (2020) | Aim: <i>To assess current clinical effectiveness of primary prevention ICD therapy.</i> |

| | |
|---------------------------|---|
| | <p>Study: 2327 patients with ischaemic or dilated cardiomyopathy and guideline indications for prophylactic ICD implantation. Primary endpoint was all-cause mortality. Primary prophylactic ICD treatment was associated with a 27% lower mortality after adjustment. There appear to be patients with less survival advantage, such as older patients or diabetics.</p> |
| PRESERVE-EF (2019) | <p>Aim: To assess if an arrhythmic risk stratification protocol successfully identifies patients with EF \geq 40% post-MI who might benefit from ICD due to high risk of ventricular arrhythmia.</p> <p>Study: 204 post-MI ischaemia-free patients, with LVEF \geq 40% with at least one positive ECG non-invasive risk factor: PVCs, non-sustained VT, late potentials, prolonged QTc, increased T-wave alternans, reduced heart rate variability, abnormal deceleration capacity with abnormal turbulence, were referred for programmed ventricular stimulation, with ICDs offered to those inducible. The primary endpoint was the occurrence of a major arrhythmic event, namely sustained VT/VF, appropriate ICD activation or SCD. The two-step approach of the PRESERVE EF study detects a subpopulation of post-MI patients with preserved LVEF at risk for MAEs that can be effectively addressed with an ICD.</p> |
| DAVID (2002) | <p>Aim: To determine the efficacy of dual-chamber pacing compared with backup ventricular pacing in patients with standard indications for ICD implantation but without indications for antibradycardia pacing.</p> <p>Study: 506 patients with LVEF \leq 40%, no indication for antibradycardia pacemaker therapy, and no persistent atrial arrhythmias, but with indications for ICD therapy were enrolled. Dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for heart failure.</p> |
| WRAP-IT (2019) | <p>Aim: To evaluate the safety and effectiveness of the envelope in reducing CIED infection as adjunctive therapy to standard strategies.</p> <p>Study: 6983 patients undergoing placement of a CIED were randomized to an absorbable antibiotic-eluting envelope versus control. All patients received preprocedure intravenous antibiotics and sterile technique.</p> |

| | |
|--------------------------|--|
| | <i>Adjunctive use of an antibacterial envelope resulted in a significantly lower incidence of major CIED infections than standard-of-care infection-prevention strategies alone, without a higher incidence of complications.</i> |
| PRAETORIAN (2020) | <p>Aim: <i>To evaluate whether the subcutaneous ICD would be noninferior to the transvenous ICD with regard to short-term and long-term device-related complications and inappropriate shocks.</i></p> <p>Study: <i>849 patients with an indication for an ICD but no indications for pacing were assigned to receive a subcutaneous ICD or transvenous ICD. The primary endpoint was the composite of device-related complications and inappropriate shocks. In patients with indication for ICD but no indication for pacing, the subcutaneous ICD was noninferior to the transvenous ICD with respect to device-related complications and inappropriate shocks.</i></p> |
| OPTIC (2006) | <p>Aim: <i>To determine whether amiodarone plus beta-blocker or sotalol are better than beta-blocker alone for prevention of ICD shocks.</i></p> <p>Study: <i>412 patients who had received an ICD within 21 days for inducible or spontaneously occurring VT/VF were randomized to treatment for 1 year with amiodarone plus β-blocker, sotalol alone, or β-blocker alone. Despite use of advanced ICD technology and treatment with a β-blocker, shocks occur commonly in the first year after ICD implant. Amiodarone plus β-blocker is effective for preventing these shocks and is more effective than sotalol but has an increased risk of drug-related adverse effects.</i></p> |

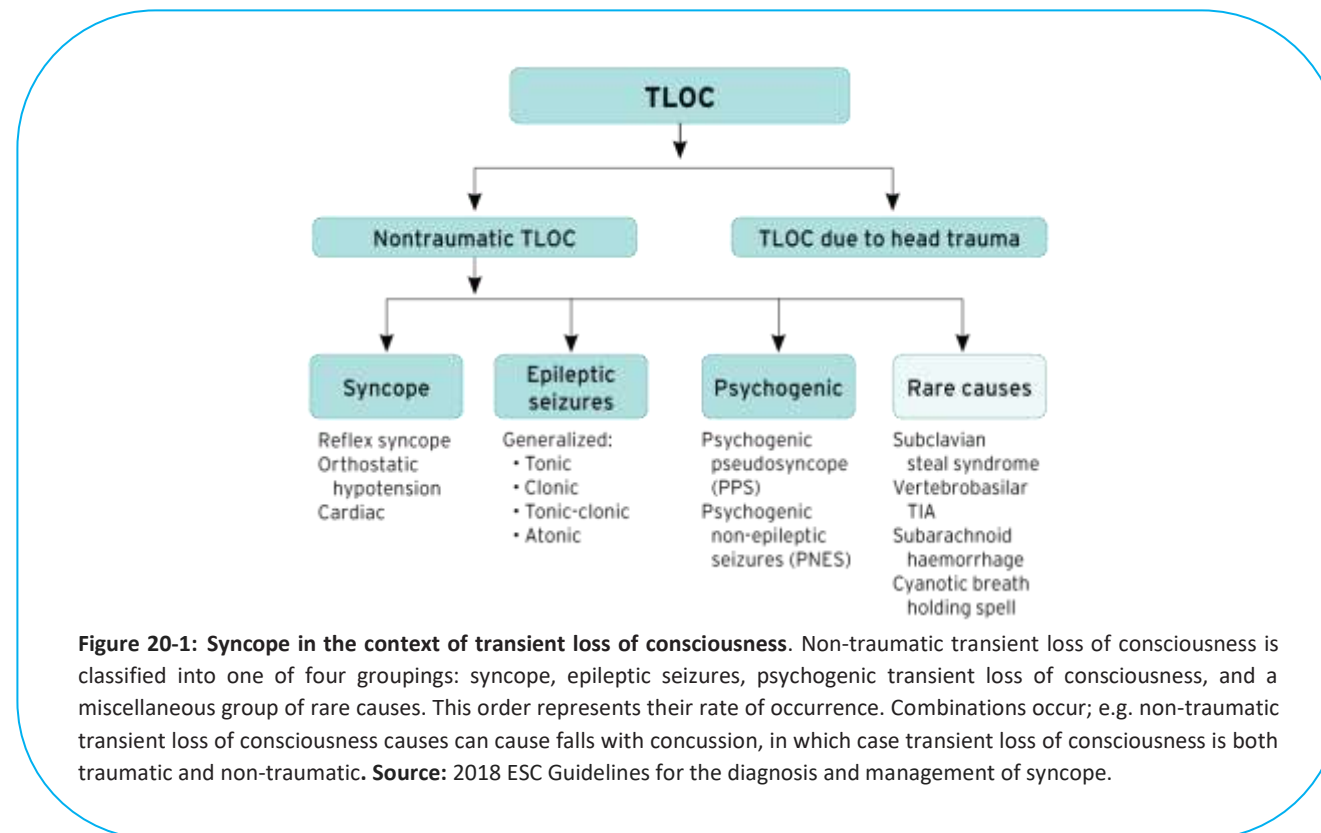
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Chapter 20:

Syncope

Transient loss of consciousness (TLOC) is a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.



Definition of syncope:

Syncope is TLOC due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.

Classification of syncope:

A. Neurally mediated syncope (Reflex syncope):

Reflex syncope is the most common type of syncope, accounting for two-thirds of the cases. It results from an *inappropriate response of autonomic reflexes, leading to vasodilatation and bradycardia*.

It is usually preceded by premonitory symptoms (lightheadedness, diaphoresis, nausea, malaise, abdominal discomfort, tunnel vision). However, this may not be the case in a third of patients, more so elderly patients. Palpitations are frequently reported with reflex syncope and do not necessarily imply an arrhythmic syncope. This syncope does not usually occur in a supine position, but may occur in a seated position. Subtypes of neurally mediated syncope are as follows:

- **Vasovagal syncope:**

This syncope is usually triggered by sudden emotional stress, prolonged sitting or standing, dehydration, or a warm environment, but may also occur without any trigger. Usually, it is preceded and followed by nausea, malaise, fatigue, or diaphoresis; the patient's full revival may be slow and malaise may persist for hours. When the syncope is prolonged > 30-60 sec, clonic movements and loss of bladder control are common.

Mechanism: Emotional stress, reduced venous return (from dehydration or prolonged standing), or vasodilatation (hot environment) stimulates the sympathetic system and reduces the LV cavity size, which leads to strong hyperdynamic contractions in a relatively empty heart. This hyperdynamic cavity obliteration activates the myocardial mechanoreceptors C, initiating a paradoxical vagal reflex with vasodilatation (vasodepressor response) and relative bradycardia (cardioinhibitory response).

- **Situational syncope:**

This syncope is caused by a reflex triggered in specific circumstances such as micturition, defecation, coughing, weightlifting, laughing, or deglutition. The reflex may be initiated by a receptor on the visceral wall (e.g., bladder wall) or by the strain that reduces venous return.

- **Carotid sinus syndrome:**

Spontaneous carotid sinus syndrome is a form of carotid sinus hypersensitivity (CSH) where syncope clearly occurs in a situation that stimulates the carotid sinus (head rotation, head extension, shaving, tight collar); this is a rare cause of syncope (~1% of syncope cases).

Conversely, induced carotid sinus syndrome is much more common and represents CSH in a patient with unexplained syncope and without obvious triggers; the abnormal response is induced during carotid massage rather than spontaneously. In induced carotid sinus syndrome, CSH is a marker of a diseased SA or AV node that cannot withstand any inhibition; this diseased node is the true cause of syncope rather than CSH per se, and carotid massage is a “stress test” that unveils conduction disease.

- **Post-exertional syncope:**

While exertional syncope is alarming for a malignant cardiac cause, post-exertional syncope is usually a form of vasovagal syncope. Upon exercise cessation, venous blood stops getting pumped back to the heart through the peripheral muscular contraction, yet the heart is still exposed to the catecholamine surge and hypercontracts on an empty cavity.

Post-exertional syncope may also be seen in HOCM and AS, where the small LV cavity is less likely to tolerate the reduced preload after exercise and is more likely to obliterate.

B. Orthostatic hypotension and postural orthostatic tachycardia syndrome:

- **Orthostatic hypotension:** (~10% of cases of syncope)

Normally, after the first few minutes of standing, ~25-30% of blood pools in the veins of the pelvis and the lower extremities, reducing venous return and stroke volume. This normally leads to a reflex increase of sympathetic tone, peripheral and splanchnic vasoconstriction, and increased heart rate.

Orthostatic hypotension is defined as a drop of SBP ≥ 20 or DBP ≥ 10 mmHg after 30 sec to 3 min of orthostasis ⁽¹⁾ (due to autonomic dysfunction and lack of compensatory increase in SVR or heart rate).

Along with the BP drop, a failure to increase heart rate (< 15 bpm) identifies autonomic dysfunction. On the other hand, an excessive increase in heart rate > 20 -30 bpm may signify a hypovolemic state even if BP is maintained, the lack of BP drop being related to the excessive heart rate increase.

Orthostatic hypotension is the most common cause of syncope in the elderly and may be due to: **(i)** autonomic dysfunction (age, diabetes, CKD, TTR amyloidosis, paraneoplastic syndrome, Parkinson disease), **(ii)** volume depletion, **(iii)** drugs that block autonomic effects or cause hypovolemia (vasodilators, β -blockers, diuretics, neuropsychiatric medications, alcohol).

- **Postural orthostatic tachycardia syndrome (POTS):**

POTS is another form of orthostatic failure that occurs most frequently in young women (< 50 years old). POTS is defined as a striking increase in rate of ≥ 30 bpm within 5 to 10 min of standing, with no significant drop in BP (< 20 mmHg). Unlike in orthostatic hypotension, BP and cardiac output are maintained through this increase in heart rate, yet the patient still develops symptoms of severe fatigue or near-syncope, because of flow maldistribution and reduced cerebral flow.

- c. **Cardiac syncope:** (~ 10 -20% of cases of syncope)

Cardiac syncope is the main concern in patients presenting with syncope, and the main predictor of mortality and sudden death. Syncope often occurs suddenly without any warning signs. There are three forms of cardiac syncope:

- **Structural heart disease** with cardiac obstruction: AS, HOCM, severe pulmonary arterial hypertension. Peripheral vasodilatation occurs during exercise, but CO cannot increase because of the fixed or dynamic obstruction to the ventricular outflow. BP drops with the reduction in vascular resistance.
- **Ventricular tachycardia** secondary to structural heart disease, or primary electrical disease.
- **Bradyarrhythmias**, usually due to degeneration of the conduction system or to medications, rather than cardiomyopathies.

(1) Some patients may have an immediate BP drop of > 40 mmHg upon standing, with a quick return to normal within 30 sec. This “initial orthostatic hypotension” may be common in elderly patients receiving antihypertensive drugs.

Pathophysiology:

The pathophysiological classification centres on a fall in systemic blood pressure with a decrease in global cerebral blood flow as the defining characteristic of syncope. A sudden cessation of cerebral blood flow for as short as 6-8 s can cause complete LOC. A systolic BP of 50-60 mmHg at heart level, i.e. 30-45 mmHg at brain level in the upright position, will cause LOC.

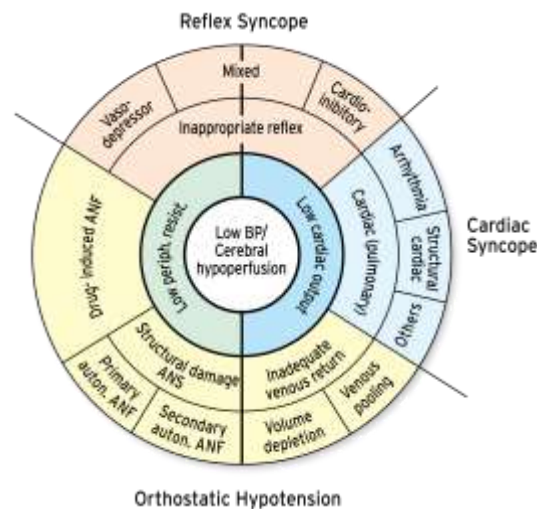
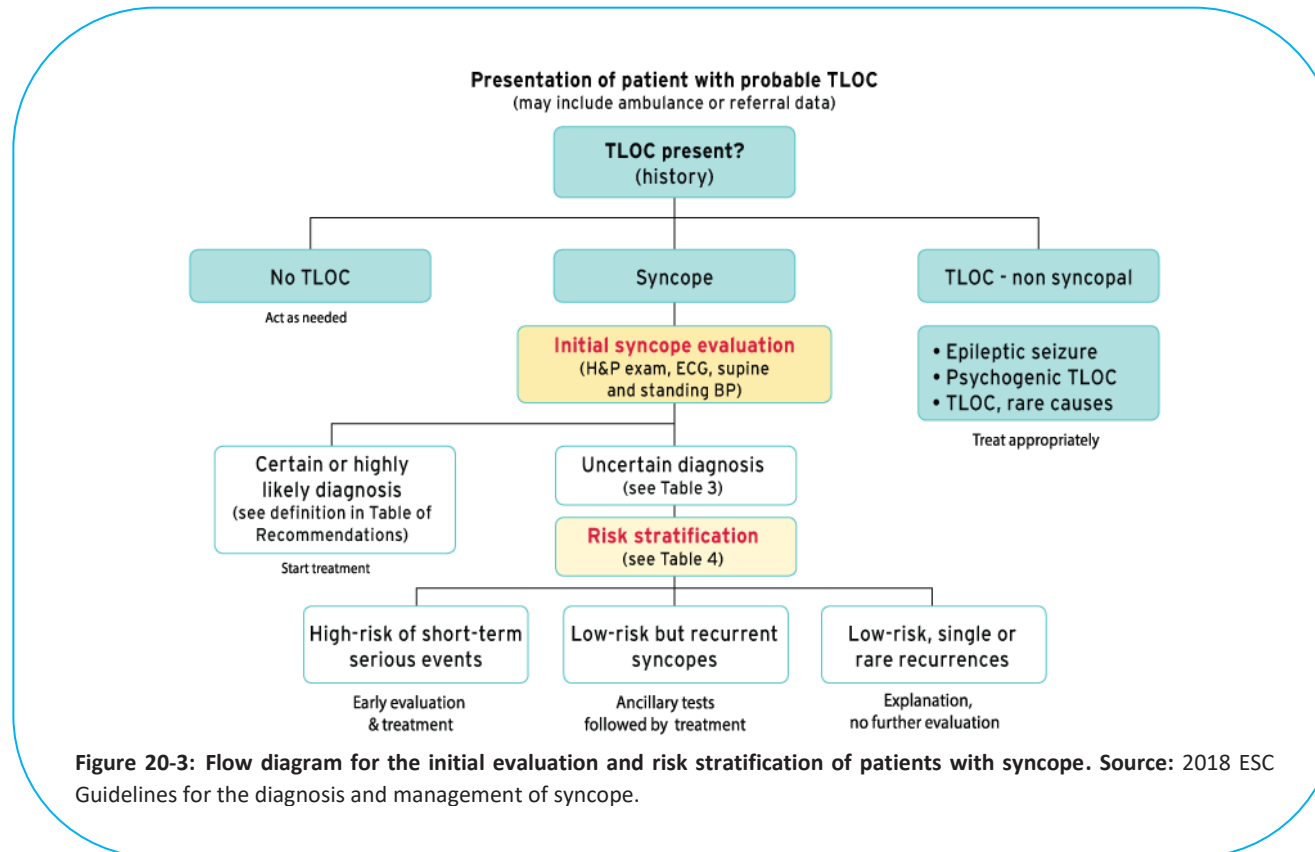


Figure 20-2: Pathophysiological basis of the classification of syncope. Source: 2018 ESC Guidelines for the diagnosis and management of syncope.

Initial Evaluation:

▪ The initial evaluation should answer key questions:

1. In case of TLOC, is it of syncopal or non-syncopal origin?
2. In case of suspected syncope, is there a clear aetiological diagnosis ?
3. Is there evidence to suggest a high risk of CV events or death ?



1. In case of TLOC, is it of syncopal or non-syncopal origin?

| Table 20-1: Conditions which may be incorrectly diagnosed as syncope: | |
|---|--|
| Condition | Characteristic Features |
| Generalized seizures | <ul style="list-style-type: none"> - Unconsciousness often lasts longer than 5 min. - Postictal confusion or paralysis |

| | |
|--|--|
| | <p>- <i>Prolonged tonic-clonic movements.</i> <i>Clonic movements may be seen with any prolonged syncope (> 30 sec), but in syncope it is more localized and brief (< 15 sec), without the tonic back arching.</i></p> <p>- <i>Tongue biting strongly suggests seizure.</i> <i>Urinary incontinence is not helpful, as it frequently occurs with syncope as well as seizure.</i></p> |
| Absence seizures | <i>No falls, yet unresponsive and later amnesia</i> |
| PPS or “pseudocoma” | <i>Duration of apparent LOC lasting many minutes to hours; high frequency, up to several times a day</i> |
| Falls without TLOC | <i>No unresponsiveness or amnesia</i> |
| Cataplexy | <i>Falls with flaccid paralysis and nonresponsive, yet no later amnesia</i> |
| Intracerebral or subarachnoid haemorrhage | <i>Consciousness may be progressively reduced rather than immediately lost. Accompanying severe headache, other neurological signs</i> |
| Vertebrobasilar TIA | <i>Always focal neurological signs and symptoms, usually without LOC; if consciousness is lost this usually lasts longer than in TLOC.</i> |
| Carotid TIA | <i>Consciousness is for all practical purposes not lost in carotid TIAs, but there are pronounced focal neurological signs and symptoms</i> |
| Subclavian steal syndrome | <i>Severe proximal subclavian disease leads to reversal of the flow in the ipsilateral vertebral artery as blood is shunted toward the upper extremity. It manifests as dizziness and syncope during the ipsilateral upper extremity activity, usually with focal neurological signs.</i> |
| Metabolic disorders e.g., hypoglycaemia, hypoxia | <i>Duration much longer than in TLOC; consciousness may be impaired instead of lost</i> |

| | |
|-----------------------|--|
| Intoxication | |
| Coma | <i>Duration much longer than TLOC</i> |
| Cardiac arrest | <i>LOC yet no spontaneous recovery</i> |

2. In case of suspected syncope, is there a clear aetiological diagnosis?

Underlying structural heart disease is the most important predictor of ventricular arrhythmias and death. Thus, the primary goal of syncope evaluation is to rule out structural heart disease.

Initial syncope evaluation include:

- **Basic evaluation:** Careful history taking concerning present and previous attacks (including eyewitness accounts), Physical examination (including supine and standing BP measurements), ECG (normal ECG, or mild non-specific ST-T abnormality, suggests a low likelihood of cardiac syncope and is associated with an excellent prognosis).
- **Additional evaluation:**
 - Immediate ECG monitoring when there is a suspicion of arrhythmic syncope.
 - Echocardiogram when there is previous known heart disease, data suggestive of structural heart disease, or syncope secondary to cardiovascular cause.
 - Carotid sinus massage (CSM) in patients aged > 40 years. Carotid massage is contraindicated if the patient has a carotid bruit or any history of stroke.
 - Head-up tilt testing when there is suspicion of syncope due to OH or reflex syncope.
 - Blood tests when clinically indicated, e.g., haematocrit or haemoglobin when haemorrhage is suspected, oxygen saturation and blood gas analysis when hypoxia is suspected, troponin when cardiac ischaemia-related syncope is suspected, or D-dimer when pulmonary embolism is suspected, etc.

Table 20-2: Clinical features that can suggest a diagnosis on initial evaluation:

Clinical clues:

○ **Position during syncope:**

- Supine → reflex syncope is unlikely
- Sitting or standing position → any cause is possible.
- Within a few minutes of standing → orthostatic hypotension
- Prolonged sitting or standing → vasovagal

○ **Situation during syncope:**

- Exertion (strenuous activity, not just walking) → cardiac syncope (cardiac obstacle, ventricular arrhythmias)
- Post-exertion → vasovagal
- Postprandial → orthostatic hypotension
- Sudden fear, pain, unpleasant sight, hot environment → vasovagal
- Strain situation (micturition) → reflex syncope
- Head turning, shaving, tight collar → carotid sinus syndrome.

○ **Prodromes** (abdominal discomfort, malaise, palpitations, nausea, blurry vision)

- Yes and > 5 seconds → reflex syncope.
- No or < 5 seconds → reflex or cardiac syncope. Reflex or orthostatic syncope may be associated with prodromes < 5 seconds or no prodrome in 33-50% of patients, more so in the elderly.

○ **How consciousness is regained after syncope?**

- Promptly → cardiac syncope
- Prolonged fatigue or nausea after syncope → reflex syncope
- Confusion → seizure

○ **Color during syncope:**

- Pale, diaphoresis → reflex syncope, orthostatic syncope
- Blue → arrhythmia, seizure

○ **Duration:**

- > 5 minutes → seizure, hypoglycemia; not syncope (except occasionally aortic stenosis)
- Underlying heart disease, chest pain → cardiac syncope
- Multiple neuropsychiatric or blood pressure medications → reflex or orthostatic syncope
- The presence or the lack of injury does not help differentiate cardiac from reflex syncope.
- Multiple syncopal recurrences (≥ 3) suggest a reflex or orthostatic syncope (one is less likely to survive three spells of cardiac syncope). This is particularly true if the interval between spells is > 4 years.

ECG or rhythm monitor findings suggestive of cardiac syncope:

- Bradyarrhythmia-related syncope is established with any of the following:
 - Sinus bradycardia < 40 bpm or sinus pauses > 3 s while awake, unless in a setting of high vagal tone or vasovagal mechanism
 - Mobitz II or complete AV block.
 - Alternating LBBB or RBBB (on the same ECG or on ECGs obtained on separate occasions)
- Bradyarrhythmia-related syncope is suggested with:
 - Isolated RBBB or LBBB (VT also possible, depending on the underlying cardiac disease)
 - Mobitz type I AV block
- Tachyarrhythmia-related syncope is established with: Sustained VT or fast SVT (> 160 bpm)
- Underlying heart disease and VT are suggested with:
 - AF
 - Q waves
 - LBBB, RBBB, QRS > 110 ms
 - LVH, RVH, large R wave in V1
- Primary electrical disorders are suggested with: Long QTc, pre-excitation, Brugada pattern, or T-wave inversion in V₁-V₃ or epsilon waves (ARVD)
- Acute ST-T abnormalities

Table 20-3: ESC recommendations for Diagnostic criteria with initial evaluation:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Reflex syncope and OH: | | |
| <i>Vasovagal syncope is highly probable if syncope is precipitated by pain, fear, or standing, and is associated with typical progressive prodrome (pallor, sweating, and/or nausea).</i> | I | C |
| <i>Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers.</i> | I | C |
| <i>Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant significant OH.</i> | I | C |
| <i>In the absence of the above criteria, reflex syncope and OH should be considered likely when the features that suggest reflex syncope or OH are present and the features that suggest cardiac syncope are absent.</i> | IIa | C |
| Cardiac syncope: | | |
| <p>Arrhythmic syncope is highly probable when the ECG shows:</p> <ul style="list-style-type: none"> - Persistent sinus bradycardia < 40 b.p.m. or sinus pauses > 3 s in awake state and in absence of physical training. - Mobitz II second- and third-degree AV block. - Alternating left and right BBB. - VT or rapid paroxysmal SVT. - Non-sustained episodes of polymorphic VT and long or short QT interval; or - Pacemaker or ICD malfunction with cardiac pauses. | I | C |

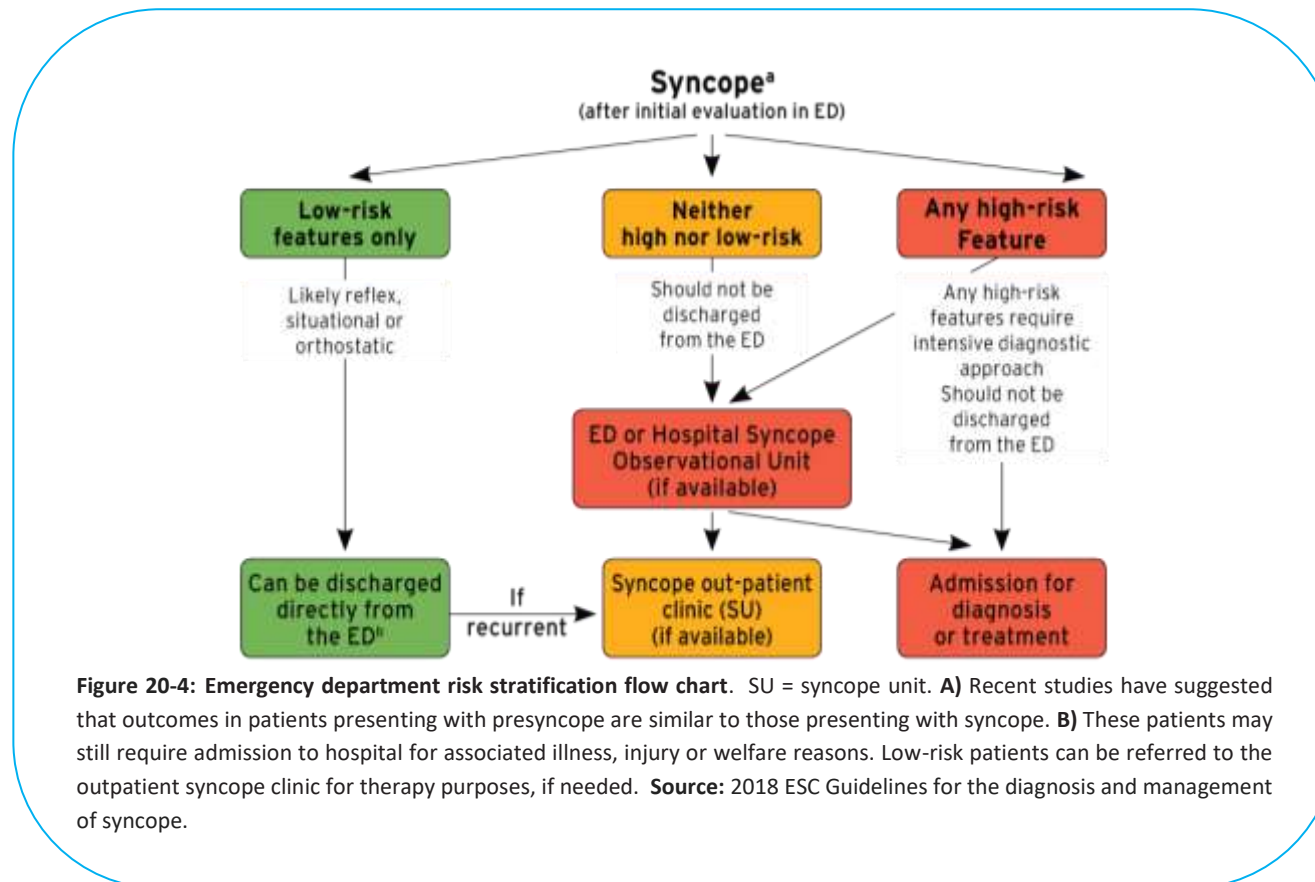
| | | |
|--|----------|----------|
| <i>Cardiac ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction.</i> | I | C |
| <i>Syncope due to structural cardiopulmonary disorders is highly probable when syncope presents in patients with prolapsing atrial myxoma, left atrial ball thrombus, severe aortic stenosis, pulmonary embolus, or acute aortic dissection.</i> | I | C |

3. Is there evidence to suggest a high risk of CV events or death?

| Table 20-4: High-risk features in patients with syncope at initial evaluation: |
|---|
| Syncopal events: |
| <ul style="list-style-type: none"> • Major: <ul style="list-style-type: none"> ○ <i>New onset of chest discomfort, breathlessness, abdominal pain, or headache</i> ○ <i>Syncope during exertion or when supine</i> ○ <i>Sudden onset palpitation followed by syncope</i> • Minor (<i>high risk only if associated with structural heart disease or abnormal ECG</i>): <ul style="list-style-type: none"> ○ <i>No warning symptoms or short (< 10s) prodrome</i> ○ <i>Family history of SCD at young age</i> ○ <i>Syncope in the sitting position</i> |
| Past medical history: |
| <ul style="list-style-type: none"> ○ <i>Severe structural or coronary artery disease (heart failure, Low EF or previous MI)</i> |
| Physical Examination: |
| <ul style="list-style-type: none"> ○ <i>Unexplained systolic blood pressure in the ED < 90 mmHg</i> ○ <i>Suggestion of GI bleed on rectal examinations</i> ○ <i>Persistent bradycardia (< 40 b.p.m) in awake state and in absence of physical training</i> |

| ○ <i>Undiagnosed systolic murmur</i> | |
|---|--|
| ECG: | |
| Major | Minor (high risk if only consistent with arrhythmic syncope) |
| <ul style="list-style-type: none"> ○ <i>ECG changes consistent with acute ischemia</i> ○ <i>Mobitz II second- and third- degree AV block</i> ○ <i>Slow AF (< 40 b.p.m)</i> ○ <i>Persistent sinus bradycardia (< 40 b.p.m) or repetitive pauses > 3 sec in awake state and in absence of physical training</i> ○ <i>Bundle branch block, intraventricular conduction disturbance, LVH or Q waves consistent with IHD or cardiomyopathy</i> ○ <i>Sustained and non-sustained VT</i> ○ <i>Dysfunction of pacemaker or ICD</i> ○ <i>Type 1 burgada pattern</i> ○ <i>QTc > 460 ms in repeated ECGs indicating LQTS.</i> | <ul style="list-style-type: none"> ○ <i>Mobitz I second degree AV block and first-degree AV block with markedly prolonged PR interval</i> ○ <i>Asymptomatic inappropriate mild sinus bradycardia (40-50 b.p.m), or slow AF (40-50 b.p.m)</i> ○ <i>Paroxysmal SVT or AF</i> ○ <i>Pre-exicted QRS complex</i> ○ <i>Short QTc interval (≤ 340 ms)</i> ○ <i>Atypical Burgada patterns</i> ○ <i>Negative T wave in right precordial leads, epsilon waves suggestive ARVC</i> |

▪ **Risk Stratification:**



▪ **Criteria for hospital admission:**

Patients should be hospitalized if: **(i)** they have severe hypovolemia or bleeding, **or (ii)** if there is any suspicion of heart disease by history, examination, or ECG. In these situations, there is concern about arrhythmia, structural heart disease, or acute myocardial ischemia. The patient is admitted for immediate telemetry monitoring; echocardiography and sometimes stress testing are performed. Then the patient is discharged within 24 hours if this initial workup does not suggest underlying heart disease. Alternatively, EP study is performed or a device is placed in patients found to have structural heart disease. Prolonged

rhythm monitoring or tilt table testing may be performed when syncope with underlying heart disease or worrisome features remains unexplained.

| Table 20-5: ESC recommendations for Management of syncope in the emergency department | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>It is recommended that patients with low-risk features, likely to have reflex or situational syncope, or syncope due to OH, are discharged from the ED.</i> | I | B |
| <i>It is recommended that patients with high-risk features receive an early intensive and prompt evaluation in a syncope unit or in an ED observation unit (if available), or are hospitalized.</i> | I | B |
| <i>It is recommended that patients who have neither high- nor low-risk features are observed in the ED or in a syncope unit instead of being hospitalized.</i> | I | B |
| <i>Risk stratification scores may be considered for risk stratification in the ED.</i> | IIb | B |
| Additional advice and clinical perspectives: <ul style="list-style-type: none"> ○ <i>In the ED, presyncope should be managed as syncope; as it carries the same prognosis.</i> ○ <i>Diagnostic radiology and laboratory tests such as chest X-ray, brain CT, routine blood hematology, biochemistry, and D-dimer and cardiac markers have a low diagnostic yield, impact on risk stratification of patients with syncope, and should not routinely be used unless specifically suggested by clinical evaluation.</i> ○ <i>Around 10% of patients with syncope in the ED will suffer from a serious outcome within 7-30 days of their visit, with just under half occurring after their stay in the ED.</i> ○ <i>To reduce inappropriate admissions, patients who have a cardiac device and syncope should undergo prompt device interrogation.</i> ○ <i>Risk stratification scores perform no better than good clinical judgement and should not be used alone to perform risk stratification in the ED.</i> | | |

Additional Diagnostic tests:

▪ **Carotid sinus massage:**

- Carotid sinus massage is indicated in patients > 40 years of age with unexplained syncope. It consists of applying firm pressure over each carotid bifurcation (just below the angle of the jaw) consecutively for 10 sec. It is performed at the bedside, and may be performed in both supine and erect positions during tilt table testing; erect positioning increases the sensitivity of carotid massage.
- CSM should not be undertaken in patients with previous TIA, stroke, or known carotid stenosis. Carotid auscultation should be performed before CSM. If a carotid bruit is present, carotid ultrasound should be performed to exclude carotid disease.
- An abnormal response to carotid sinus massage is defined as any of the following:
 - Vasodepressor response: SBP decreases by ≥ 50 mmHg and/or
 - Cardioinhibitory response: pause ≥ 3 sec (sinus pause or AV block).
- History of syncope and its reproduction by CSM defines CSS; positive CSM without a history of syncope defines carotid sinus hypersensitivity.
- Carotid sinus hypersensitivity in patients with unexplained syncope may be a non-specific finding because it is present in $\leq 40\%$ of older populations and should be used with caution for diagnosis of the mechanism of syncope.

Table 20-6: ESC recommendations for Carotid sinus massage:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Indications: | | |
| <i>CSM is indicated in patients > 40 years of age with syncope of unknown origin compatible with a reflex mechanism.</i> | I | B |
| Diagnostic criteria: | | |

CSS is confirmed if CSM causes bradycardia (asystole) and/or hypotension that reproduce spontaneous symptoms, and patients have clinical features compatible with a reflex mechanism of syncope.

I B

▪ **Active standing:**

| Table 20-7: ESC recommendations for Active standing: | | |
|--|------------|----------|
| Recommendations | Class | Level |
| Indications: | | |
| Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 min are indicated at initial syncope evaluation. | I | C |
| Continuous beat-to-beat non-invasive BP and HR measurement may be preferred when short-lived BP variations are suspected, such as in initial OH. | IIb | C |
| Diagnostic criteria: | | |
| Syncope due to OH is confirmed when there is a fall in systolic BP from baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, or a decrease in systolic BP to < 90 mmHg that reproduces spontaneous symptoms. | I | C |
| Syncope due to OH should be considered likely when there is a symptomatic fall in systolic BP from baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, or a decrease in systolic BP to < 90 mmHg, and not all of the features (from history) are suggestive of OH. | IIa | C |
| Syncope due to OH should be considered likely when there is an asymptomatic fall in systolic BP from baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, or a decrease in systolic BP to < 90 mmHg, and symptoms (from history) are consistent with OH. | IIa | C |

| | | |
|--|------------|----------|
| <i>Syncope due to OH may be considered possible when there is an asymptomatic fall in systolic BP from baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, or a decrease in systolic BP to < 90 mmHg, and symptoms (from history) are less consistent with OH.</i> | IIb | C |
| <i>POTS should be considered likely when there is an orthostatic HR increase (> 30 b.p.m. or to > 120 b.p.m. within 10 min of active standing) in the absence of OH that reproduces spontaneous symptoms.</i> | IIa | C |

▪ **Tilt testing:**

- Tilt testing consists of strapping the patient to a table that is subsequently inclined to 60-80° for 30-45 min. It is a form of orthostatic stress that simulates prolonged standing and is actually more stressful than standing, as the patient is deprived of the skeletal muscle pumping that normally occurs with standing.
- The specificity of tilt table testing for vasovagal syncope is up to 90% and the false positive rate is ~10%. The false-positive rate is higher in patients with structural heart disease; in fact, tilt table testing elicits syncope in up to 25% of patients with arrhythmic syncope and abnormal EP study.
- The yield of tilt testing is highest in patients with an intermediate pre-test probability of vasovagal syncope, such as patients without structural heart disease who have an unexplained malignant or recurrent syncope, elderly patients with unexplained syncope or fall, **or** patients with structural heart disease (e.g., treated CAD, LVH) but normal or only mildly reduced EF and normal EP study. Patients with a high or low pre-test probability of vasovagal syncope have the lowest yield from tilt testing.
- **Types of response to tilt table testing:**
 - Normal response: heart rate increases by 10-15 bpm and DBP increases by > 10 mmHg.
 - Vasodepressor response: abrupt, rapid hypotension without significant drop in heart rate ($< 10\%$).
 - Cardioinhibitory response: hypotension with a drop in heart rate to < 40 bpm **or** a pause > 3 sec.
 - Mixed response: HR decreases during syncope but does not reach < 40 bpm, or reaches < 40 bpm for < 10 sec., with or without asystole < 3 sec.

In all forms of vasovagal syncope, except some cardioinhibitory forms, BP falls before the heart rate falls. BP falls suddenly.

- Initial orthostatic hypotension: Decrease in BP > 40 mmHg at standing with spontaneous and fast normalization, so that hypotension and symptoms last < 30 sec.
- Classic orthostatic hypotension: Decrease in systolic BP \geq 20 mmHg and diastolic BP \geq 10 mmHg during the first 3 min after standing. The drop in blood pressure is more gradual in orthostatic hypotension than in vasovagal syncope.
- Late (progressive) orthostatic hypotension: Slow and progressive systolic BP decline after the 3rd min of standing.
- POTS: significant increase in heart rate during the first 10 min of tilt (an increase of \geq 30 bpm, often to > 120 bpm). Significant hypotension does not occur (blood pressure is normal or low normal).
- Cerebral syncope: no significant hemodynamic change, but intense cerebral vasoconstriction on transcranial Doppler.
- Psychogenic syncope: syncope without hemodynamic or transcranial Doppler change.

Table 20-8: ESC recommendations for Tilt testing:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Indications: | | |
| <i>Tilt testing should be considered in patients with suspected reflex syncope, OH, POTS, or PPS.</i> | IIa | B |
| <i>Tilt testing may be considered to educate patients to recognize symptoms and learn physical manoeuvres.</i> | IIb | B |
| Diagnostic criteria: | | |
| <i>Reflex syncope, OH, POTS, or PPS should be considered likely if tilt testing reproduces symptoms along with the characteristic circulatory pattern of these conditions.</i> | IIa | B |

▪ **Echocardiography:**

- For patients without suspected cardiac disease after history taking, physical examination, and ECG, suggesting that syncope alone is not an indication for echocardiography.
- Computed tomography or MRI should be considered in selected patients presenting with syncope of suspected cardiac structural origin when echocardiography is not diagnostic.

Table 20-9: ESC recommendations for Role of echocardiography in the assessment of syncope:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Indications: | | |
| <i>Echocardiography is indicated for diagnosis and risk stratification in patients with suspected structural heart disease.</i> | I | B |
| <i>Two-dimensional and Doppler echocardiography during exercise in the standing, sitting, or semi-supine position to detect provokable LVOT obstruction is indicated in patients with HCM, a history of syncope, and resting or provoked peak instantaneous LVOT gradient < 50 mmHg.</i> | I | B |
| Diagnostic criteria: | | |
| <i>Aortic stenosis, obstructive cardiac tumours or thrombi, pericardial tamponade, and aortic dissection are the most probable causes of syncope when the ECG shows the typical features of these conditions.</i> | I | C |

▪ **Electrophysiological study:**

- EP study is valuable for patients with structural heart disease, including EF 36-49%, CAD, AF, or LVH with normal EF. EPS is not useful in patients with syncope, normal ECG, no heart disease, and no palpitations.
- In general, whereas a positive EPS predicts the cause of syncope, a negative study is unable to exclude an arrhythmic syncope and further evaluation is warranted.
- The induction of polymorphic VT or VF in patients with ischemic cardiomyopathy or DCM cannot be considered a diagnostic finding of the cause of syncope.

Table 20-10: ESC recommendations for Role of Electrophysiological study in the management of syncope:

| Recommendations | Class | Level |
|------------------------|--------------|--------------|
| Indications: | | |

| | | |
|--|------------|----------|
| <i>In patients with syncope and previous myocardial infarction, or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation.</i> | I | B |
| <i>In patients with syncope and bifascicular BBB, EPS should be considered when syncope remains unexplained after non-invasive evaluation.</i> | IIa | B |
| <i>In patients with syncope and asymptomatic sinus bradycardia, EPS may be considered in a few instances when non-invasive tests (e.g. ECG monitoring) have failed to show a correlation between syncope and bradycardia.</i> | IIb | B |
| <i>In patients with syncope preceded by sudden and brief palpitations, EPS may be considered when syncope remains unexplained after non-invasive evaluation.</i> | IIb | C |
| EPS-guided therapy: | | |
| <i>In patients with unexplained syncope and bifascicular BBB, a pacemaker is indicated in the presence of either a baseline H-V interval of ≥ 70 ms, second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge.</i> | I | B |
| <i>In patients with unexplained syncope and previous myocardial infarction, or other scar related conditions, it is recommended that induction of sustained monomorphic VT is managed according to the current ESC Guidelines for VA.</i> | I | B |
| <i>In patients without structural heart disease with syncope preceded by sudden and brief palpitations, it is recommended that the induction of rapid SVT or VT, which reproduce hypotensive or spontaneous symptoms, is managed with appropriate therapy according to the current ESC Guidelines.</i> | I | C |
| <i>In patients with syncope and asymptomatic sinus bradycardia, a pacemaker should be considered if a prolonged corrected SNRT is present.</i> | IIa | B |

- **Basic autonomic function tests:** Autonomic function assessment helps to identify autonomic failure as the underlying cause of syncope.

| Table 20-11: ESC recommendations for Basic autonomic function tests: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Valsalva manoeuvre: | | |
| <i>Valsalva manoeuvre should be considered for the assessment of autonomic function in patients with suspected neurogenic OH.</i> | IIa | B |
| <i>Valsalva manoeuvre may be considered for confirming the hypotensive tendency induced by some forms of situational syncope, e.g. coughing, brass instrument playing, singing, and weightlifting.</i> | IIb | C |
| Deep-breathing test: | | |
| <i>Deep-breathing tests should be considered for the assessment of autonomic function in patients with suspected neurogenic OH.</i> | IIa | B |
| Other autonomic function tests: | | |
| <i>Other autonomic function tests (30:15 ratio, cold pressure test, sustained hand grip test, and mental arithmetic test) may be considered for the assessment of autonomic function in patients with suspected neurogenic OH.</i> | IIb | C |
| ABPM: | | |
| <i>ABPM is recommended to detect nocturnal hypertension in patients with autonomic failure.</i> | I | B |
| <i>ABPM should be considered to detect and monitor the degree of OH and supine hypertension in daily life in patients with autonomic failure.</i> | IIa | C |
| <i>ABPM and HBPM may be considered to detect whether BP is abnormally low during episodes suggestive of orthostatic intolerance.</i> | IIb | C |
| • Clinical perspectives: | | |

- Whenever possible, reproduction of the trigger situation (e.g., coughing, swallowing, laughing, bass instrument playing, weightlifting) under beat to-beat non-invasive HR and BP measurement should be performed in patients with suspected situational syncope.
- The effects of age and sex should be considered when interpreting autonomic function tests.
- Compliance with autonomic function tests may be limited in patients with dementia. Patients with tremor or Parkinsonism may not succeed in performing the sustained hand grip test. The cold pressure test may be uncomfortable in patients with Raynaud's phenomena.

▪ **ECG monitoring (Non-invasive and Invasive):**

| Table 20-12: ESC recommendations for ECG monitoring: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Indications: | | |
| <i>Immediate in-hospital monitoring (in bed or by telemetry) is indicated in high-risk patients.</i> | I | C |
| <i>Holter monitoring should be considered in patients who have frequent syncope or presyncope (≥ 1 episode per week).</i> | IIa | B |
| <i>External loop recorders should be considered, early after the index event, in patients who have an inter-symptom interval ≤ 4 weeks.</i> | IIa | B |
| <i>ILR is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria, and a high likelihood of recurrence within the battery life of the device.</i> | I | A |
| <i>ILR is indicated in patients with high-risk criteria in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have conventional indications for primary prevention ICD or pacemaker indication.</i> | I | A |

| | | |
|--|------------|----------|
| <i>ILR should be considered in patients with suspected or certain reflex syncope presenting with frequent or severe syncopal episodes.</i> | IIa | B |
| <i>ILR may be considered in patients in whom epilepsy was suspected but the treatment has proven ineffective.</i> | IIb | B |
| <i>ILR may be considered in patients with unexplained falls.</i> | IIb | B |
| Diagnostic criteria: | | |
| <i>Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected.</i> | I | B |
| <i>In the absence of syncope, arrhythmic syncope should be considered likely when periods of Mobitz II second- or third-degree AV block or a ventricular pause > 3 s (with the possible exception of young trained persons, during sleep or rate controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected.</i> | IIa | C |
| <p>• Clinical perspectives</p> <ul style="list-style-type: none"> - Be aware that the pre-test selection of the patients influences the subsequent findings. The duration of monitoring should be selected according to the risk and the predicted recurrence rate of syncope. - Exclude patients with a clear indication for ICD, pacemaker, or other treatments independent of a definite diagnosis of the cause of syncope. - Include patients with a high likelihood of arrhythmic events. - Include patients with a high probability of recurrence of syncope in a reasonable time. Owing to the unpredictability of syncope recurrence, be prepared to wait up to 4 years or more before obtaining such a correlation. - In the absence of a documented arrhythmia, presyncope cannot be considered a surrogate for syncope, whereas the documentation of a significant arrhythmia at the time of presyncope can be considered a diagnostic finding. | | |

- The absence of arrhythmia during syncope excludes arrhythmic syncope.

▪ **Video recording in suspected syncope:**

Table 20-13: ESC recommendations for Video recording in suspected syncope:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Home video recordings of spontaneous events should be considered. Physicians should encourage patients and their relatives to obtain home video recordings of spontaneous events.</i> | IIa | C |
| <i>Adding video recording to tilt testing may be considered in order to increase the reliability of clinical observation of induced events.</i> | IIb | C |

▪ **Exercise testing:** There is no data supporting routine exercise testing in patients with syncope.

Table 20-14: ESC recommendations for Role of exercise testing in the assessment of syncope:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Indications: | | |
| <i>Exercise testing is indicated in patients who experience syncope during or shortly after exertion.</i> | I | C |
| Diagnostic criteria: | | |
| <i>Syncope due to second- or third-degree AV block is confirmed when the AV block develops during exercise, even without syncope.</i> | I | C |
| <i>Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension.</i> | I | C |

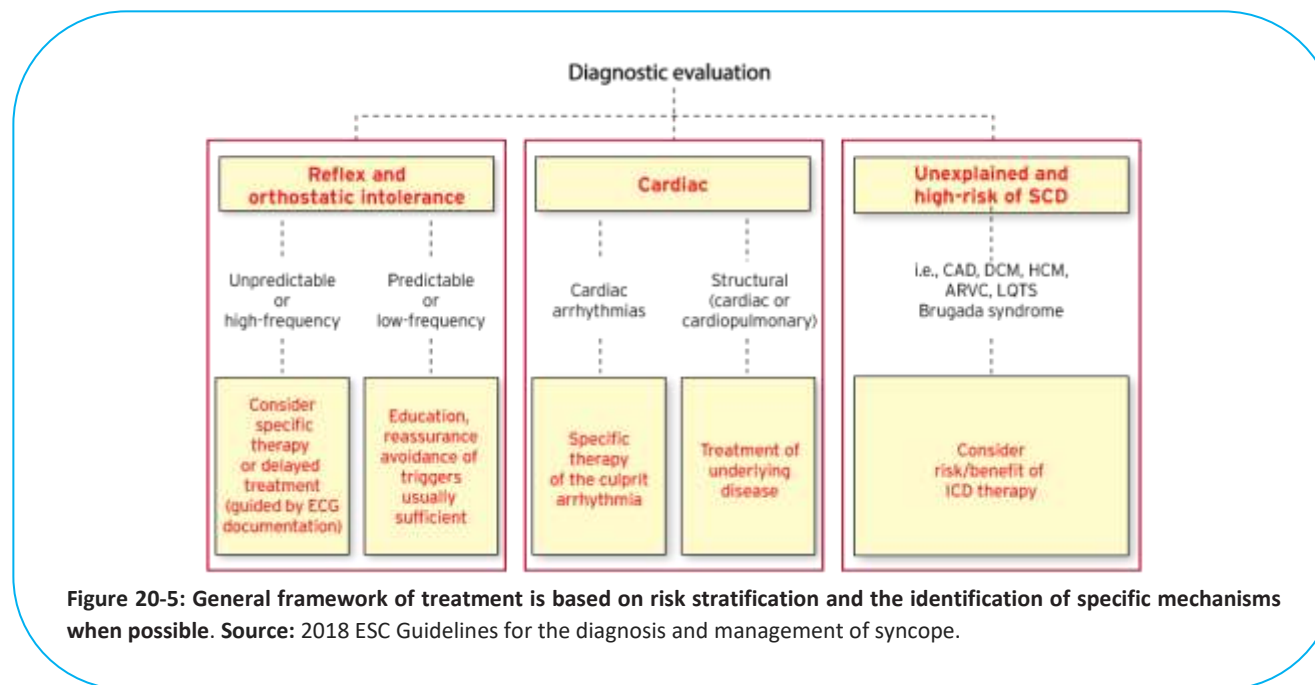
▪ **Coronary angiography:** Angiography alone is not diagnostic of the cause of syncope.

Table 20-15: ESC recommendations for Role of coronary in the assessment of syncope:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with syncope, the same indications for coronary angiography should be considered as in patients without syncope.</i> | IIa | C |

Treatment:

The general framework of treatment is based on risk stratification and the identification of specific mechanisms when possible. The efficacy of therapy aimed at preventing syncope recurrence is largely determined by the mechanism of syncope rather than its aetiology.



- **Treatment of reflex syncope:** Despite its benign course, recurrent and unpredictable reflex syncope may be disabling. In general, no therapy can completely prevent syncope recurrence during long-term follow-up. A decrease of the syncope burden is a reasonable goal of therapy.
- The cornerstone of management of these patients is non-pharmacological treatment, including **education, lifestyle modification, and reassurance** regarding the benign nature of the condition.
- Additional treatment may be necessary in patients with severe forms, in particular: **(i)** when very frequent syncope alters quality of life; **(ii)** when recurrent syncope without, or with a very short, prodrome exposes the patient to a risk of trauma; and **(iii)** when syncope occurs during a high-risk activity (e.g. driving, machine operation, flying, or competitive athletics, etc.). This includes:
 - **Physical counterpressure maneuvers (PCM):** PCM are movements that promote cardiovascular stability and aim to prevent peripheral pooling of blood by decreasing orthostatic load (e.g. sitting down), shortening the hydrostatic column between the heart and the brain (e.g. bending the head), and/or increasing the central blood flow by generating a mechanical compression of the veins (e.g. leg crossing).
 - Discontinuation/reduction of hypotensive therapy targeting a systolic BP of 140 mmHg.
 - **Pharmacological treatment:**
 - Fludrocortisone (mineralocorticoid), by increasing renal sodium reabsorption and expanding plasma volume, may counteract the physiological cascade leading to the orthostatic vasovagal reflex. The mechanism of action can be compared with that of saline infusion, which has also proved effective in acute tilt test studies. Fludrocortisone should be titrated at a dosage of 0.05–0.2 mg once per day. Fludrocortisone should not be used in patients with hypertension or heart failure.
 - Midodrine (α -agonist) [usually 2.5-10 mg, t.i.d] has proved effective in small studies. The most frequent side effects were supine hypertension, pilomotor reactions, and urinary problems (urinary retention, hesitancy, or urgency). The major limitation of midodrine is frequent dosing, which limits the compliance.
 - **Role of Pacing:** Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Pacing is indicated in patients aged ≥ 40 with recurrent unpredictable syncopes if there is:

- Asystolic pauses (3s cutoff for pauses coinciding with symptoms, 6s for asymptomatic pauses, 3s for symptomatic tilt pauses).
- Carotid sinus syndrome, which is a syncope occurring when the carotid sinus is manipulated, along with a cardioinhibitory response to carotid sinus massage, is an indication for dual-chamber pacing.
- Unexplained syncope with a cardioinhibitory carotid sinus hypersensitivity is an indication for dual-chamber pacing.
- Patients with adenosine-sensitive syncope: characterized by abrupt AV block or sinus arrest with an otherwise normal heart, no conduction disease on ECG/EP, and often negative tilt test. Those patients have very low plasma adenosine levels and a high induction rate of pauses > 6 s when injected with adenosine. This syncope may qualify for pacing, but it is best to document pauses on loop recorder, which eventually happen in ~50% of the cases.

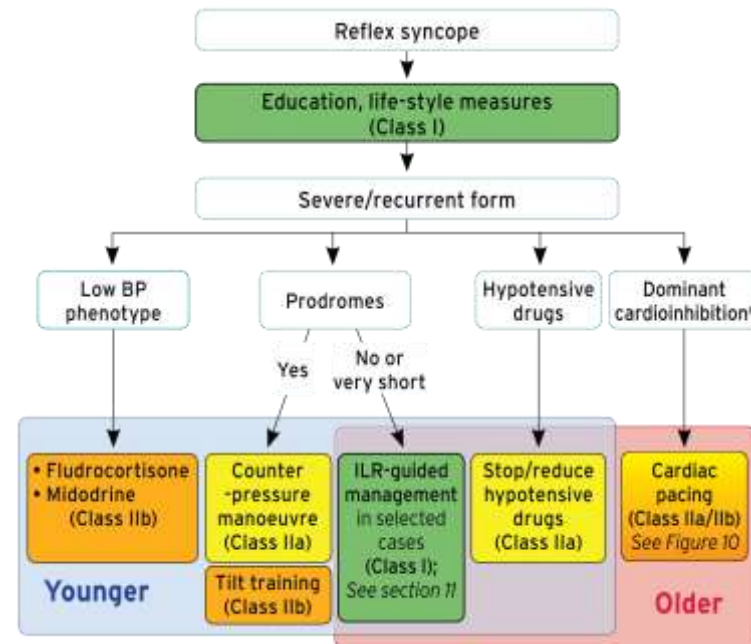


Figure 20-6: Schematic practical decision pathway for the first-line management of reflex syncope.

Younger patients are those aged < 40 years while older patients are > 60 years, with an overlap between 40 and 60 years. The heading 'low BP phenotype' identifies patients with chronic low BP values (in general, SBP around 110 mmHg, who have a clear history of orthostatic intolerance and orthostatic VVS). The group 'dominant cardioinhibition' identifies patients in whom clinical features and results of tests suggest that sudden cardioinhibition is mainly responsible for syncope. Patients with short or no prodrome should continue investigations to identify the underlying mechanism and guide subsequent therapy. ILR = implantable loop recorder; VVS = vasovagal syncope. **A)** Spontaneous or provoked by, sequentially, carotid sinus massage, tilt testing, or ILR. **Source:** 2018 ESC Guidelines for the diagnosis and management of syncope.

Pacing for reflex syncope: decision pathway

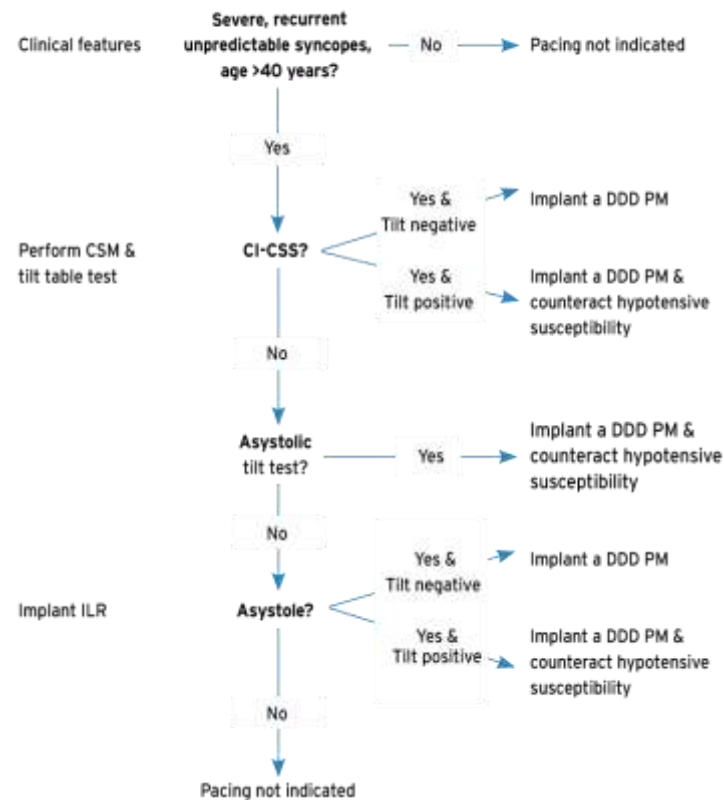


Figure 20-7: Decision pathway for cardiac pacing in patients with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome; CSM = carotid sinus massage; DDD PM = dual-chamber pacemaker; ILR = implantable loop recorder. **Source:** 2018 ESC Guidelines for the diagnosis and management of syncope.

Table 20-16: ESC recommendations for Management of reflex syncope:

Recommendations

Class Level

| | | |
|--|------------|----------|
| Education and lifestyle modifications: | | |
| <i>Explanation of the diagnosis, the provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients.</i> | I | B |
| Discontinuation/reduction of hypotensive therapy: | | |
| <i>Modification or discontinuation of hypotensive drug regimen should be considered in patients with vasodepressor syncope, if possible.</i> | IIa | B |
| Physical manoeuvres: | | |
| <i>Isometric physical counterpressure maneuvers (PCM) should be considered in patients with prodromes who are < 60 years of age.</i> | IIa | B |
| <i>Tilt training may be considered for the education of young patients.</i> | IIb | B |
| Pharmacological therapy: | | |
| <i>Fludrocortisone (mineralocorticoid) may be considered in young patients with the orthostatic form of VVS, low-normal values of arterial BP, and the absence of contraindication to the drug.</i> | IIb | B |
| <i>Midodrine (α-agonist) may be considered in patients with the orthostatic form of VVS.</i> | IIb | B |
| <i>Beta-adrenergic blocking drugs are not indicated.</i> | III | A |
| Cardiac pacing: | | |
| <i>Cardiac pacing should be considered to reduce syncopal recurrences in patients aged > 40 years with:</i> <ul style="list-style-type: none"> <i>- spontaneous documented symptomatic asystolic pause(s) > 3 s <u>or</u> asymptomatic pause(s) > 6 s due to sinus arrest, AV block, or the combination of the two.</i> <i>- cardioinhibitory carotid sinus syndrome with recurrent frequent unpredictable syncope.</i> | IIa | B |
| <i>Cardiac pacing may be considered to reduce syncope recurrences in patients with tilt-induced asystolic response who are > 40 years with recurrent frequent unpredictable syncope.</i> | IIb | B |

| | | |
|--|------------|----------|
| <i>Cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope.</i> | IIb | B |
| <i>Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.</i> | III | B |

▪ **Treatment of orthostatic hypotension and orthostatic intolerance syndromes:**

- Maintain good fluid intake (2-3 L/day) and salt intake (> 3 g/day; 10 g/day in young POTS patients). Avoid large meals high in fat and complex carbohydrates and avoid exertion after eating.
- In individuals with established OH and risk factors for falls, aggressive BP-lowering treatment should be avoided; their treatment targets should be revised to a systolic BP value of 140-150 mmHg and medication withdrawal should be considered. The BP-lowering agents (ACEIs, ARBs, and CCBs) should be used preferentially, as diuretics and beta-blockers are associated with OH and falls and should be avoided in at-risk individuals.
- Both POTS and orthostatic hypotension are often related to CV deconditioning. Regular, progressive exercise training over a period of 3 months leads to remission of POTS in the majority of patients. To be tolerated, upright exercises may initially be avoided, with a focus on swimming, or seated biking.
- If the above fails, one of 3 medications may be used temporarily until the benefit from the exercise program kicks in: **(i)** fludrocortisone (may worsen supine HTN), **(ii)** midodrine (may worsen supine HTN, avoid it after 6 PM), and **(iii)** pyridostigmine (works on cholinergic sympathetic ganglionic transmission).
- Another option for orthostatic hypotension is droxidopa which gets metabolized into norepinephrine at the sympathetic ganglions. It is only approved for neurogenic orthostatic hypotension and may conversely aggravate the sympathetic activation in POTS.

N.B: Pyridostigmine and droxidopa effects are particularly expected during periods of sympathetic activation, such as the upright position, hence both of the two agents are much less likely to cause supine hypertension than midodrine.

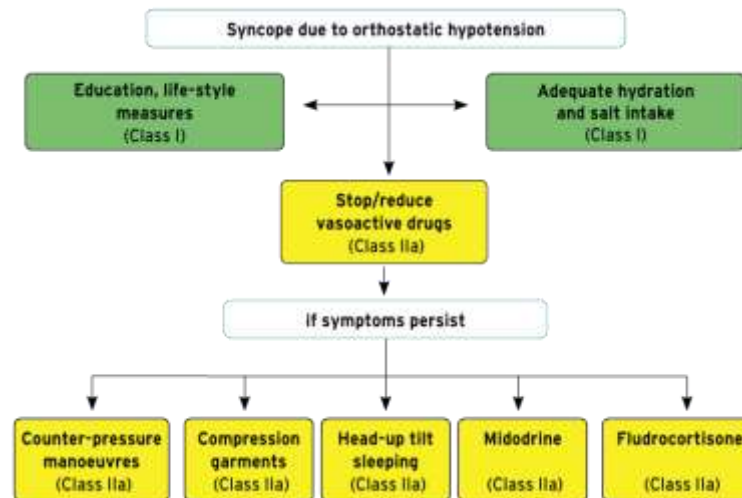


Figure 20-8: Schematic practical guide for the treatment of orthostatic hypotension. Source: 2018 ESC Guidelines for the diagnosis and management of syncope.

Table 20-17: ESC recommendations for Management of orthostatic hypotension:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Explanation of the diagnosis, the provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients.</i> | I | C |
| <i>Adequate hydration and salt intake are indicated.</i> | I | C |
| <i>Modification or discontinuation of hypotensive drug regimens should be considered.</i> | IIa | B |
| <i>Isometric PCM should be considered.</i> | IIa | C |
| <i>Abdominal binders and/or support stockings to reduce venous pooling should be considered.</i> | IIa | B |
| <i>Head-up tilt sleeping (>10 degrees) to increase fluid volume should be considered.</i> | IIa | C |
| <i>Midodrine should be considered if symptoms persist.</i> | IIa | B |

Fludrocortisone should be considered if symptoms persist.

Ila

C

References and suggested readings:

- Michele Brignole, Angel Moya, Frederik J de Lange, et al, 2018 ESC Guidelines for the diagnosis and management of syncope, *European Heart Journal*, Volume 39, Issue 21, 01 June 2018, Pages 1883–1948
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Section

V

Pericardial Diseases

TO THE POINT

Chapter 21:

Pericardial Diseases

Table 21-1: ESC Recommendations for the general diagnostic work-up of pericardial diseases:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In all cases of suspected pericardial disease, a first diagnostic evaluation is recommended with:</i> <ul style="list-style-type: none"> - Auscultation - ECG - Transthoracic echocardiography - Chest X-ray - Routine blood tests, including markers of inflammation (i.e., CRP and/or ESR), white blood cell count with differential count, renal function and liver tests and myocardial lesion tests (CK, troponins) | I | C |
| <i>It is recommended to search for independent predictors of an identifiable and specifically treatable cause of pericarditis (i.e. bacterial, neoplastic, systemic inflammatory diseases).</i> <i>Major factors include:</i> <ul style="list-style-type: none"> - fever - subacute course (symptoms developing over several days or weeks) - large pericardial effusion (diastolic echo-free space >20 mm in width) - cardiac tamponade - failure of aspirin or NSAIDs | I | B |
| <i>CT and/or CMR are recommended as second-level testing for diagnostic workup in pericarditis</i> | I | C |
| <i>Pericardiocentesis or surgical drainage are indicated for cardiac tamponade or suspected bacterial and neoplastic pericarditis</i> | I | C |

| | | |
|--|------------|----------|
| <i>Percutaneous or surgical pericardial biopsy may be considered in selected cases of suspected neoplastic or tuberculous pericarditis</i> | IIb | C |
| <i>Further testing is indicated in high-risk patients (defined as above) according to the clinical conditions</i> | I | C |

Pericarditis

Aetiology:

- **The four most common causes are:**

1. *Viral or idiopathic pericarditis* is the most common form of acute pericarditis (80–90%).
2. *Metastatic cancer*, where a moderate or large effusion is usually seen.
3. *Connective tissue disease* (lupus, rheumatoid arthritis, scleroderma).
4. *Infections* (HIV, tuberculosis, bacterial, fungal, Lyme disease). In patients with HIV infection, pericarditis may be secondary to HIV itself **or** to a concomitant infection, particularly tuberculosis.

- **Other common causes of pericarditis, occurring in specific contexts:**

1. *Uremia*: an effusion is seen in > 50 % of patients with uremic pericarditis.
2. *Radiation*: acute pericarditis, with or without effusion, may develop soon after radiation.
3. *Post-MI*: pericarditis can occur early post-MI or late (Dressler syndrome).
4. *Post-cardiac surgery*: pericarditis may occur early (in the first few days) or late (between 2 weeks and 2 months, similarly to Dressler syndrome and called *post-pericardiotomy syndrome*).
5. *Trauma* (blunt or penetrating).

Table 21-2: Aetiology of pericardial diseases.

Infectious causes:

- **Viral (common):** Enteroviruses (coxsackieviruses, echoviruses), herpes viruses (EBV, CMV, HHV-6), adenoviruses, parvovirus B19 (possible overlap with aetiological viral agents of myocarditis).
- **Bacterial:** *Mycobacterium tuberculosis* (common, other bacterial rare), *Coxiella burnetii*, *Borrelia burgdorferi*, rarely: *Pneumococcus* spp, *Meningococcus* spp, *Gonococcus* spp, *Streptococcus* spp, *Staphylococcus* spp, *Haemophilus* spp, *Chlamydia* spp, *Mycoplasma* spp, *Legionella* spp, *Leptospira* spp, *Listeria* spp, *Providencia stuartii*.
- **Fungal (very rare):** *Histoplasma* spp (more likely in immunocompetent patients), *Aspergillus* spp, *Blastomyces* spp, *Candida* spp (more likely in immunocompromised host).
- **Parasitic (very rare):** *Echinococcus* spp, *Toxoplasma* spp

Non-infectious causes:

- **Autoimmune (common):** SLE, Sjögren syndrome, rheumatoid arthritis, scleroderma, systemic vasculitides (i.e. eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, giant cell arteritis also known as Horton disease, Takayasu disease, Behçet syndrome), sarcoidosis, familial.
- **Neoplastic:**
 - Primary tumours (rare, above all pericardial mesothelioma).
 - Secondary metastatic tumours (common, above all lung and breast cancer, lymphoma).
- **Metabolic:** Uraemia, myxoedema, anorexia nervosa, other rare.

Traumatic:

- **Early onset (rare):**
 - Direct injury (penetrating thoracic injury, esophageal perforation).
 - Indirect injury (non-penetrating thoracic injury, radiation injury).

- **Delayed onset:** Pericardial injury syndromes (common; such as postmyocardial infarction syndrome, postpericardiotomy syndrome), posttraumatic (including forms after iatrogenic trauma e.g. PCI, pacemaker lead insertion and radiofrequency ablation).

Drug-related:

- Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin).
- Antineoplastic drugs (often associated with a cardiomyopathy, may cause a pericardiopathy): doxorubicin, daunorubicin.
- Penicillins as a hypersensitivity pericarditis with eosinophilia.
- Others: amiodarone, methysergide, mesalazine, clozapine, minoxidil, dantrolene, practolol, phenylbutazone, thiazides, streptomycin, thiouracils, streptokinase, p-aminosalicylic acid, sulfa drugs, cyclosporine, bromocriptine, several vaccines, GM-CSF, anti-TNF agents.

Others:

- Common: Amyloidosis, Aortic dissection, PAH and HF.
- Uncommon: congenital partial and complete absence of the pericardium.

It is not mandatory to search for the aetiology in all patients, especially in countries with a low prevalence of TB, because of the relatively benign course associated with the common causes of pericarditis and the relatively low yield of diagnostic investigations. On this basis, a triage for acute pericarditis is proposed.

Any clinical presentation that may suggest an underlying aetiology (e.g. systemic inflammatory disease) or with at least one predictor of poor prognosis (major or minor risk factors) warrants hospital admission and an aetiology search. The specific etiologic workup consists of: HIV testing, Purified protein derivative (PPD), ANA/rheumatoid factor, screening for specific cancers. On the other hand, patients without these features can be managed as outpatients with empiric antiinflammatories and short-term follow-up after 1 week to assess the response to treatment.

Predictors of poor prognosis:

- **Major:**

- High fever > 38 C.
- Subacute course (symptoms over several days without a clear-cut acute onset).
- Large pericardial effusion (i.e. diastolic echo-free space > 20 mm).
- Cardiac tamponade.
- Failure to respond within 7 days to NSAIDs.

- **Minor:**

- Myopericarditis.
- Immunodepression
- Trauma
- Oral anticoagulant therapy.

Types:

Table 21-3: Definitions and diagnostic criteria for pericarditis:

| Type of pericarditis | Definition and diagnostic criteria |
|----------------------|--|
| Acute | <i>Inflammatory pericardial syndrome to be diagnosed with at least 2 of the following 4 criteria:</i> <i>6. Pericardial chest pain</i> <i>7. Pericardial rubs</i> <i>8. New widespread ST-elevation or PR depression on ECG</i> <i>9. Pericardial effusion (new or worsening)</i> <i>Additional supporting findings:</i> |

| | |
|------------------|--|
| | <ul style="list-style-type: none"> ○ Elevation of markers of inflammation (i.e CRP, ESR and WBCs) ○ Evidence of pericardial inflammation by an imaging technique (CT, CMR) |
| Incessant | <i>Pericarditis lasting for > 4-6 weeks but < 3 months without remission</i> |
| Recurrent | <i>Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4-6 weeks or longer</i> |
| Chronic | <i>Pericarditis lasting for > 3 months</i> |

Diagnosis:

The diagnosis of pericarditis requires two of the following four features:

1. Chest pain:

- Chest pain is sharp, pleuritic, usually not constricting. It usually has a rapid, sometimes abrupt, onset. It radiates to the trapezius ridge (a typical radiation of pericarditis) and/or the left arm.
- Positional feature: pain is relieved by leaning forward and worsens with lying down, swallowing, or moving (including exertion).

2. Rub:

- The rub is due to the friction of the inflamed visceral and parietal pericardial layers.
- It is heard during systole, early diastolic filling, and atrial contraction (three components). It is best heard at the left lower sternal border with the patient leaning forward. A sound with a single component is less specific for pericarditis as it may actually represent a murmur.
- The rub is dynamic (it comes and goes), and all three components may not be evident all the time, hence the importance of frequent examinations when pericarditis is suspected.
- A rub may be heard with pericardial effusion when concomitant inflammatory pericarditis is present.

3. Typical ECG findings:

- **Diffuse concave ST elevation in all leads except aVR and V1:** The axis of the subepicardial injury being the axis of the heart ($\sim +45^\circ$), the ST elevation is most prominent in lead II and in the anterolateral leads, while the ST segment is often depressed in lead aVR, and sometimes V1 (orthogonal to $+45^\circ$).

The ST segment elevation normalizes in 1–5 days, often within 7 days. Thus, the ECG of pericarditis can look normal within a few days, at the time the patient presents.

The return of ST segment to baseline is followed, sometimes, by T-wave inversion that may last weeks or months. T wave may become biphasic before ST normalization, mimicking ischemia.

- **PR depression:** The PR segment is depressed in 82% of patients, and this may be the earliest change. It is seen in all leads except lead aVR, where reciprocal PR elevation is always seen. While it commonly coexists with ST elevation, it can be an isolated change in $\sim 25\%$ of patients.

ST elevation and PR depression are mainly seen in idiopathic pericarditis, post-cardiac surgery pericarditis, and traumatic and hemorrhagic pericarditis. They are rarely seen in uremic, malignant, or tuberculous pericarditis, probably because of associated processes masking the pericarditis pattern.

- **Low QRS voltage and QRS alternans:**

If an effusion is present, the ECG may show low QRS voltage and sometimes QRS electrical alternans (which means an every-other-beat alternation of two different QRS morphologies).

P- and T-wave alternans, in which two different P- and T-wave morphologies alternate, increases the likelihood of a pericardial effusion.

Sinus tachycardia associated with a low QRS voltage or QRS alternans suggests tamponade.

4. **Pericardial effusion** (Pericardial effusion is not necessary but confirms the diagnosis when present).

- Most often, No effusion is present (“dry” pericarditis).
- Small effusion is seen in 40% of pericarditis cases. Moderate or large effusions are seen in 5% of cases.
- 25–50% of moderate or large pericardial effusions are idiopathic, whereas 80–90% of pericarditis cases with no or small effusions are idiopathic.

- An effusion increases the likelihood of a specific cause, such as malignancy, infection, or connective tissue disorder.

Additional supporting findings:

- CRP is a confirmatory finding. CRP is required by some authors for the diagnosis of pericarditis and is a useful monitoring marker.
- ESR may be used but is less specific and rises and falls later than CRP. Conversely, a severely elevated ESR has a valuable diagnostic value and suggests tuberculosis or autoimmune disease.
- A low-titer ANA is very common in idiopathic pericarditis (~40%) and often does not have any clinical significance. ANA testing may be useful in high-risk pericarditis.
- Evidence of pericardial inflammation by an imaging technique (CT, MRI).

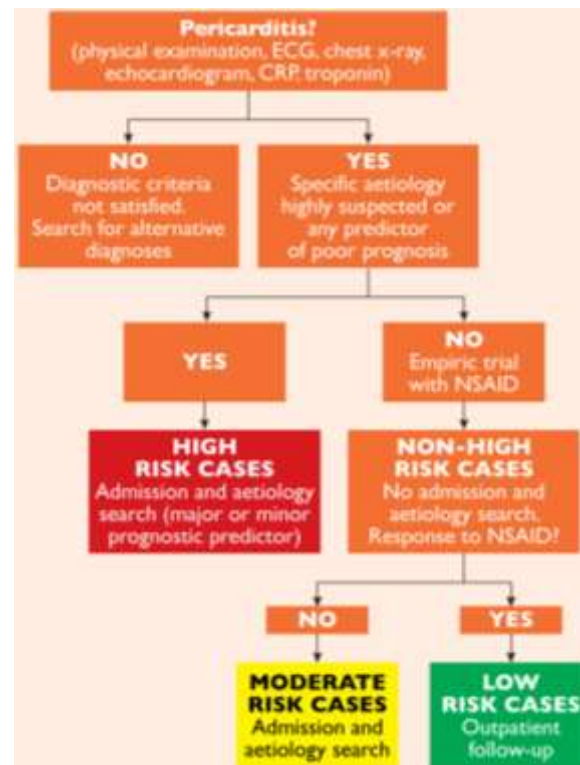


Figure 21-1: Proposed triage of pericarditis. High risk cases include those with at least one predictor of poor prognosis is sufficient to identify. Moderate risk cases include those without negative prognostic predictors but incomplete or lacking response to NSAID therapy. Low risk cases include those without negative prognostic factors and good response to anti-inflammatory therapy. **Source:** 2015 ESC Guidelines for the diagnosis and management of pericardial diseases

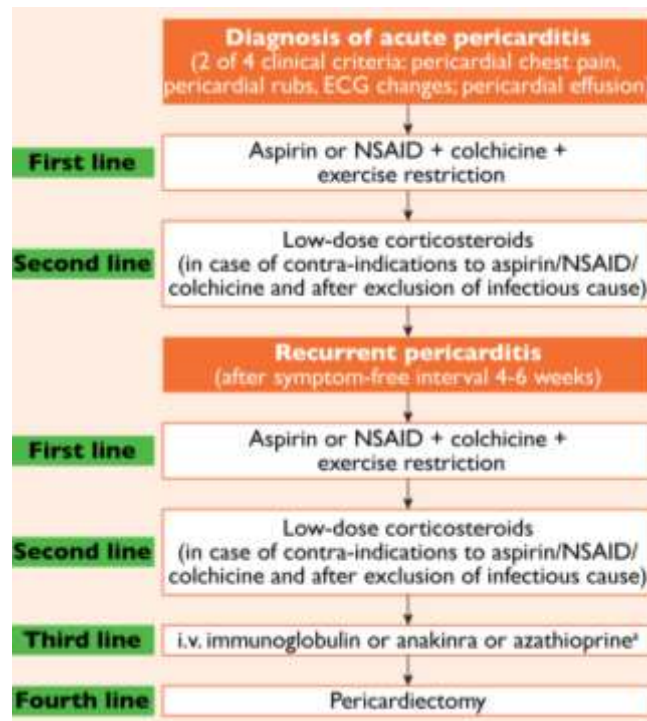


Figure 21-2: Therapeutic algorithm for acute and recurrent pericarditis. Low-dose corticosteroids are considered when there are contraindications to other drugs or when there is an incomplete response to aspirin/NSAIDs plus colchicine; in this case physicians should consider **adding** these drugs instead of replacing other anti-inflammatory therapies. **A)** Azathioprine is steroid sparing and has a slow onset of action compared with IVIG and anakinra. Cost consideration may apply considering the cheaper solution first (e.g. azathioprine) and resorting to more expensive options (e.g. IVIG and anakinra) for refractory cases. **Source:** 2015 ESC Guidelines for the diagnosis and management of pericardial diseases.

| Table 21-4: Commonly Prescribed anti-inflammatory therapy for acute pericarditis: | | | |
|--|---|--------------------------------|---|
| Drug | Usual dosing | Duration ⁽¹⁾ | Tapering |
| Aspirin | 750-1000 mg every 8 hrs | 1-2 weeks | Decrease doses by 250-500 mg ..every 1-2 weeks |
| Ibuprofen | 600 mg every 8 hrs | 1-2 weeks | Decrease doses by 200-400 mg .. every 1-2 weeks |
| Colchicine | If BW < 70kg: 0.5 mg once If BW > 70kg: 0.5 mg b.i.d | 3 months | Not mandatory |
| Prednisolone | 0.25-0.5 mg/kg/day ⁽²⁾ | | > 50 mg: 10 mg/day .. every 1-2 weeks 25-50 mg: 5-10 mg/day .. every 1-2 weeks 15-25 mg: 2.5 mg/day .. every 2-4 weeks < 15 mg: 1.25-2.5 mg/day .. every 2-6 weeks Every decrease in prednisolone dose should be done only if the patient is asymptomatic and CRP is normal, particularly for doses < 25mg/day. |

N.B: Calcium intake 1200-1500 mg/day and vitamin D 800-1200 IU/day should be offered to all patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men \geq 50 years and post menopausal women in whom long-term treatment with glucocorticoids is initiated at a dose \geq 5-7.5 mg/day of prednisolone or equivalent.

(1) Treatment duration is symptoms and CRP guided but generally 1-2 weeks for uncomplicated cases. Gastroprotection should be prescribed. Colchicine is added on top of aspirin or ibuprofen.

(2) Avoid higher doses except for special cases, and only for a few days with rapid tapering to 25 mg/day.

Prognosis:

- Pericarditis is a self-limiting disease with no complication or recurrence in > 70 % of patients.
- Cardiac tamponade rarely occurs in patients with acute idiopathic pericarditis, and is more common in patients with a specific underlying aetiology such as malignancy, TB or purulent pericarditis.
- Constrictive pericarditis may occur in <1% of patients with acute idiopathic pericarditis, and is also more common in patients with a specific aetiology. The risk of developing constriction can be classified as:
 - Low (<1%) for idiopathic and presumed viral pericarditis;
 - Intermediate (2 –5%) for autoimmune, immunemediated and neoplastic aetiologies; and
 - High (20–30%) for bacterial aetiologies, especially with TB and purulent pericarditis.
- Approximately 15–30% of patients with idiopathic acute pericarditis who are not treated with colchicine will develop either recurrent or incessant disease, while colchicine may halve the recurrence rate.

Recurrent pericarditis

- 15-30% of patients with idiopathic or autoimmune pericarditis develop recurrent pericarditis within 20 months after the initial episode, and pericarditis may keep relapsing for several years.
- It is due to an autoimmune process initiated by the initial viral infection, although persistent or recurrent infection is possible.
- In the absence of high-risk features, recurrent pericarditis is usually idiopathic and does not warrant specific workup. Moreover, recurrent idiopathic pericarditis is usually milder than the initial pericarditis and is not associated with pericardial constriction.
- One-third of patients have pleuropericardial involvement during these recurrences.
- For each recurrence, repeat the course of NSAID for a longer duration (2–4 weeks) with slow tapering over an additional 3–4 weeks, and give a course of colchicine for ≥ 6 months.

Table 21-5: ESC Recommendations for the management of recurrent pericarditis:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Aspirin and NSAIDs are mainstays of treatment and are recommended at full doses, if tolerated, until complete symptom resolution</i> | I | A |
| <i>Colchicine (0.5 mg twice daily or 0.5 mg daily for patients <70 kg or intolerant to higher doses); use for 6 months is recommended as an adjunct to aspirin/NSAIDs</i> | I | A |
| <i>Colchicine therapy of longer duration (> 6 months) should be considered in some cases, according to clinical response</i> | IIa | C |
| <i>CRP dosage should be considered to guide the treatment duration and assess the response to therapy</i> | IIa | C |
| <i>After CRP normalization, a gradual tapering of therapies should be considered, tailored to symptoms and CRP, stopping a single class of drugs at a time</i> | IIa | C |
| <i>Drugs such as IVIG, anakinra and azathioprine may be considered in cases of corticosteroid-dependent recurrent pericarditis in patients not responsive to colchicine</i> | IIb | C |
| <i>Exercise restriction should be considered for non-athletes with recurrent pericarditis until symptom resolution and CRP normalization, taking into account the previous history and clinical conditions</i> | IIa | C |
| <i>Exercise restriction for a minimum of 3 months should be considered for athletes with recurrent pericarditis until symptom resolution and normalization of CRP, ECG and echocardiogram</i> | IIa | C |
| <i>If ischaemic heart disease is a concern or antiplatelet therapy is required, aspirin should be considered, at medium high doses (1–2.4 g/day)</i> | IIa | C |
| <i>If symptoms recur during therapy tapering, the management should consider not increasing the dose of corticosteroids to control symptoms, but increasing to the maximum dose of aspirin or</i> | IIa | C |

| | | |
|---|-----|---|
| NSAIDs, well distributed, generally every 8 hours, and intravenously if necessary, adding colchicine and adding analgesics for pain control | | |
| Corticosteroid therapy is not recommended as a first line-approach | III | B |

Myopericarditis

- Various degrees of myocardial inflammation are seen in patients with pericarditis. In fact, the ST-segment elevation implies subepicardial myocardial involvement rather than just pericardial involvement (the pericardium is electrically silent). Therefore, a troponin rise is common in pericarditis (median 7ng/ml).
- *Myopericarditis* implies mild myocardial involvement, as evidenced by an elevated troponin, with a normal EF and no wall motion abnormalities. *Perimyocarditis* with mild LV dysfunction (EF 40–50%) is associated with a good long-term prognosis and persistence of LV dysfunction in only 15% of patients Vs. 60% of patients with severe LV dysfunction.
- Coronary angiography should be done to rule out ACS. Reduction of the NSAID dose is considered (e.g., aspirin 500mg TID), exercise is restricted for 6 months.

Table 21-6: ESC Recommendations for the diagnosis and management of pericarditis associated with myocarditis:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In cases of pericarditis with suspected associated myocarditis, coronary angiography (according to clinical presentation and risk factor assessment) is recommended in order to rule out acute coronary syndromes</i> | I | C |
| <i>Cardiac magnetic resonance is recommended for the confirmation of myocardial involvement</i> | I | C |
| <i>Hospitalization is recommended for diagnosis and monitoring in patients with myocardial involvement</i> | I | C |
| <i>Rest and avoidance of physical activity beyond normal sedentary activities is recommended in non-athletes and athletes with myopericarditis for a period of 6 months</i> | I | C |

Empirical anti-inflammatory therapies (lowest efficacious doses) should be considered to control chest pain

Ila

C

Pericardial effusion

A pericardial effusion without tamponade is not associated with hemodynamic compromise but may be associated with a dull ache and sometimes a pericarditic chest pain. Dyspnea on exertion may occur and is, in fact, a manifestation of early tamponade. In order to be well tolerated and asymptomatic, a large effusion must be chronic.

A large effusion is defined as an effusion larger than 2 cm related to the anterior and posterior echo-free spaces in *diastole*. This measurement is smaller in diastole than systole, but the diastolic measurement is what accounts for the diastolic compression and for the ability to tap (must be > 2–3 cm to allow a safe pericardiocentesis).

Causes:

- **Similarly to acute pericarditis, the 5 most common causes of a moderate or large effusion are:**

1. **Viral/idiopathic.** Viral/idiopathic pericarditis rarely leads to a large effusion or tamponade, yet is still the most common cause of effusion and tamponade. Approximately 30–50% of large pericardial effusions are viral/idiopathic.
2. **Neoplastic** (lung, breast, lymphoma, melanoma). Malignancy causes 20–30% of pericardial effusions. Approximately 20% of patients with tamponade of unsuspected etiology are diagnosed with malignant effusion, this being their first cancer manifestation. Tamponade is a greater predictor of malignancy than an asymptomatic effusion.

3. **Metabolic** (uremia or hypothyroidism):

In Uremic effusion: Two forms of renal pericarditis are seen:

- Uremic pericarditis: occurs in acute or advanced chronic renal failure not undergoing dialysis. It usually resolves after several weeks of intensive hemodialysis; unless tamponade is present, watchful management is appropriate ⁽¹⁾.

(1) Heparin should be used cautiously during dialysis.

- Dialysis-associated pericarditis: occurs in patients undergoing adequate chronic dialysis with normal BUN and creatinine. This effusion inconsistently responds to dialysis intensification. A pericardial window may be required.

4. Connective tissue diseases.

- 5. Specific bacterial infection or tuberculosis.** Bacterial infections can spread from contiguous sites (pneumonia, empyema, ruptured valvular abscess, thoracic surgery) or hematogenously.

• **Other causes are seen in specific contexts:**

1. Post-cardiac surgery. The effusion may be:

Early hemorrhagic effusion: occurs in the first postoperative week with a high risk of tamponade.

Late postoperative effusions: The effusion may also occur late (typically appear or progress over the first 8–10 days). These late effusions may be due to slow blood oozing in the pericardium or to a post-pericardiotomy syndrome, which is a pericardial and pleural inflammatory process occurring later than a week after surgery. In fact, half of these late effusions are hemorrhagic, while the other half are serosanguinous. It usually resolves within weeks.

In fact, by postoperative day 8, ~40% of patients have a small effusion, ~20% have a moderate effusion, and 1% have a large effusion. By postoperative day 20–30, most of these effusions resolve or improve (by 5–10mm on average), but ~10% of patients still have a moderate effusion. Large effusions have at least a 25% risk of progressing to tamponade within 30 days, while the risk with moderate effusions is ~10%; the risk may even be higher when these effusions persist longer.

During cardiac surgery, the pericardium is opened and left open, which may seem protective against the development of a pericardial effusion. In reality, the edges of the cut pericardium may adhere to the sternum and create a new pericardial space, which is bound by the sternum anteriorly and the pericardium posterolaterally and superiorly. Moreover, the parietal pericardium may adhere to the visceral pericardium, thus closing the pericardial space. Hence, half of the postoperative pericardial effusions are circumferential, more so in case of tamponade, while the other half are loculated. Most loculated effusions are either anterior (meaning, over the RV) or posterolateral. Isolated loculation over the RA is less common (LA much less common).

2. **Post-MI.** The effusion may occur early (resolves slowly over months) or late (along with Dressler syndrome). Conversely, an early moderate or large effusion suggests a threatening free wall rupture.
3. **Radiation therapy.** An early effusion (< 1 year) may occur as part of an acute pericarditis and is sometimes recurrent. A late effusion (> 1 year) is part of an effusive–constrictive pericarditis.
4. **HF or volume overload states** (*nephrotic syndrome, cirrhosis*). Pericardial effusion is usually small or moderate in size, transudative, and only develops when right heart failure is present, as the pericardial veins drain in the coronary sinus. Isolated left heart failure does not lead to a pericardial effusion.
5. **Hemorrhagic pericardial effusion:**
 - Penetrating or blunt trauma, free wall rupture post-MI, complication of PCI (coronary perforation) or complication of device implantation (RA or RV rupture).
 - Other causes: *malignant, viral, or infectious*, with a prognosis that depends on the underlying etiology.
6. **Drugs** (mainly *minoxidil* and drug-induced lupus: *hydralazine, isoniazid*).

N.B:

A large idiopathic pericardial effusion has a relatively low risk of progression to tamponade. Conversely, neoplastic, bacterial/tuberculous/HIV, and postoperative large effusions have a high risk of progression to tamponade. Hemorrhagic effusions have an imminent risk of tamponade.

Management:

General approach to Pericardial effusion:

Two main concerns dictate the management of asymptomatic effusions: **(A)** Aetiology and **(B)** Risk of progression to tamponade. The following strategy is suggested:

- In the absence of a known medical condition that could cause a pericardial effusion: Screen for some cancers, HIV/tuberculosis, and metabolic disorders using clinical findings and investigations (CXR, mammography, chest CT; PPD, HIV; TSH, renal function, rheumatoid factor, ANA).
- **Pericardiocentesis is indicated If:**
 - *Malignant or bacterial (including tuberculous)* etiology is suspected, pericardiocentesis is indicated both for its diagnostic and staging value and because of the high risk of progression to tamponade (“threatened tamponade”).
Only 50% of effusions in cancer patients are due to malignant metastasis, the remaining being induced by inflammation, obstruction of lymphatic drainage, or radiation; hence the additional diagnostic importance of pericardiocentesis in these patients.
 - *Hemorrhagic pericardial effusion* is suspected (traumatic, iatrogenic), pericardiocentesis is indicated because of the imminent risk of tamponade.
 - Increasing in size, pericardiocentesis is warranted because of the risk of tamponade.
- Check markers of inflammation (CRP, ESR), which, if elevated without any cancer/infection/autoimmune disease, suggest a pericarditic process (viral/idiopathic) and may be treated with NSAID and colchicine.
- Echo follow-up is warranted to detect improvement of the effusion, on a weekly basis initially.
- A chronic, large idiopathic effusion that persists for > 3 months has a significant risk of progression to tamponade of 33%. Thus, close echo surveillance is warranted. Alternatively, pericardial drainage may be considered for effusions persisting > 3 months because of the 33% risk of tamponade.

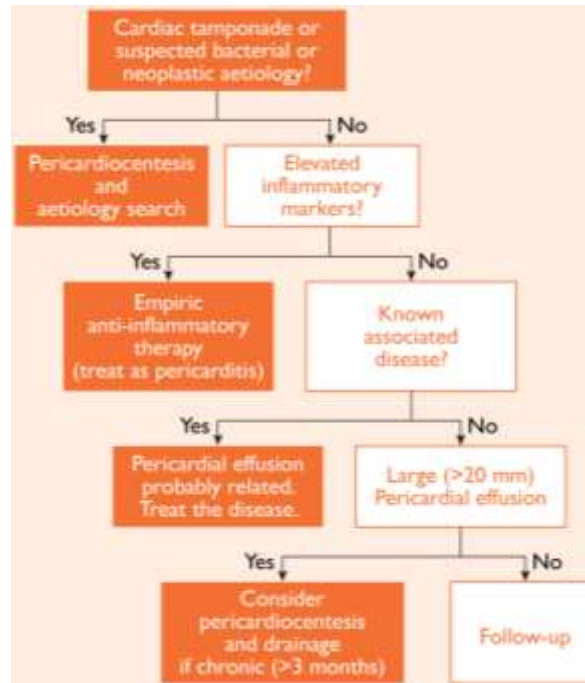


Figure 21-3: A simplified algorithm for pericardial effusion triage and management. Source: 2015 ESC Guidelines for the diagnosis and management of pericardial diseases.

| Table 21-7: ESC Recommendations for the management of pericardial effusion: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>Transthoracic echocardiography is recommended in all patients with suspected pericardial effusion.</i> | I | C |
| <i>Chest X-ray is recommended in patients with a suspicion of pericardial effusion or pleuropulmonary involvement.</i> | I | C |

| | | |
|---|------------|----------|
| <i>Assessment of markers of inflammation (i.e. CRP) are recommended in patients with pericardial effusion</i> | I | C |
| <i>CT or CMR should be considered in suspected cases of loculated pericardial effusion, pericardial thickening and masses, as well as associated chest abnormalities.</i> | IIa | C |
| Treatment: | | |
| <i>Admission is recommended for high-risk patients with pericardial effusion.</i> | I | C |
| <i>It is recommended to target the therapy of pericardial effusion at the aetiology</i> | I | C |
| <i>Aspirin/NSAIDs/colchicine and treatment of pericarditis is recommended when pericardial effusion is associated with systemic inflammation.</i> | I | C |
| <i>Pericardiocentesis or cardiac surgery is indicated for: cardiac tamponade <u>or</u> for symptomatic moderate to large pericardial effusions not responsive to medical therapy, <u>and</u> for suspicion of unknown bacterial or neoplastic aetiology</i> | I | C |

Cardiac tamponade

Definition:

Pericardial effusion compressing one or more cardiac chambers and leading to hemodynamic compromise.

Aetiology:

• Common causes:

- Pericarditis
- Tuberculosis
- Iatrogenic (invasive procedure-related, post-cardiac surgery)
- Trauma

- Neoplasm/malignancy
- **Uncommon causes:**
 - Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
 - Radiation induced
 - Postmyocardial infarction
 - Uraemia
 - Aortic dissection
 - Bacterial infection
 - Pneumopericardium

Pathophysiology and hemodynamics:

In tamponade, the pericardial fluid distends the pericardium and raises the intrapericardial pressure to ~10-25 mmHg, compressing one or more cardiac chambers. In typical, circumferential tamponade, *this high intrapericardial pressure compresses all cardiac chambers in diastole until the pressure inside the four cardiac chambers equalizes with the intrapericardial pressure.* This leads to *equalization of the diastolic pressures of the four cardiac chambers.* Since the right-sided chambers have thin walls, they tend to collapse when the intrapericardial pressure is equal to or larger than their intracavitary pressure.

In acute conditions, the pericardium cannot distend and its pressure rises markedly with small volume changes. This explains how tamponade develops with a small acute effusion (~200ml). This also explains how the pericardium gets stretched in acute RV dilatation, leading to a “functional” constrictive pericarditis. Conversely, a slowly developing pericardial effusion induces tamponade only after a large volume of fluid has accumulated.

The equalization of diastolic pressures is similar to what is observed in constrictive pericarditis. As opposed to constrictive pericarditis:

- The respiratory changes of intrathoracic pressure are transmitted to the cardiac chambers. This explains why RA pressure decreases with inspiration, and thus venous flow from outside the thorax to the RA increases during inspiration (JVP decreases, explaining the **absence of Kussmaul's sign**).

The increased venous flow to the right cavities makes the RV “push” against the LV in diastole, rather than “push” against the pericardium, since the high pericardial pressure prevents that (**ventricular interdependence**).

This reduces LV filling in normal inspiration and explains the reduction of systolic arterial pressure by > 10 mmHg with *normal* inspiration (**pulsus paradoxus**, which is an extreme form of RV–LV discordant filling).

- In constrictive pericarditis, the heart briefly expands in early diastole before getting constrained, the heart is compressed throughout all diastole in tamponade, including early diastole. Thus, there is **no deep Y** on the RA tracing and **no diastolic dip on the RV tracing**. There is a **deep X** in early systole as the RV annulus moves down and stretches out the compressed RA.

In summary, tamponade is characterized by the following three hemodynamic findings:

1. Elevation and equalization of diastolic pressures of the four cardiac chambers, similarly to constrictive pericarditis: **CVP= PCWP=** diastolic PA pressure= RVEDP= LVEDP. This equalization of diastolic pressures may also be seen in severe RV failure that creates a functional pericardial constriction.
2. Elevated RA pressure with a **deep X descent** (mainly during inspiration), and a **flat Y descent**.
3. While the systolic aortic pressure is initially normal or even elevated as a result of the adrenergic release, **pulsus paradoxus** is present and pulse pressure is abnormal early on ⁽¹⁾.

N.B:

The systolic blood pressure is initially normal or even elevated in up to one-third of tamponade cases, particularly in patients with a history of hypertension who are sensitive to the catecholamine surge. Hypertension does not imply preserved cardiac output;

(1) Example: when using the BP cuff, the Korotkoff sounds are heard intermittently at a systolic pressure of 150 mmHg and consistently at a pressure of 120; therefore, the pulsus paradoxus is 30 mmHg. Avoid deep breathing during this measurement, as deep breathing is normally associated with an inspiratory drop of aortic pressure.

but increased peripheral vascular resistance preserves arterial pressure (pressure= flow × resistance). Patients with tamponade and hypertension have a reduction in BP, reduction in systemic vascular resistance, and increase in cardiac output following pericardiocentesis.

Diagnosis: *Tamponade is a clinical diagnosis, Not an Echocardiographic diagnosis*

- **Clinical findings:** Tamponade is diagnosed when a *large pericardial effusion* is associated with *hemodynamic compromise*, i.e., any one of the following:
 1. Elevated JVP.
 2. Pulsus paradoxus, which is a decrease of SBP of > 10 mmHg during *normal, quiet inspiration*.
 3. Sinus tachycardia that attempts to compensate for the low stroke volume. Tachycardia may be absent in hypothyroidism and sometimes uremia (sinus node disease).
 4. Dyspnea/tachypnea/orthopnea with clear lungs. PCWP is increased up to 30 mmHg but the intracardiac and pulmonary venous volume is low, hence the *lack of pulmonary edema and lack of significant hypoxemia despite severe dyspnea*.
- **Echocardiographic findings:**
 1. **RV collapse in diastole.** This is the most specific echo finding in tamponade. Sometimes, just an early diastolic indentation of the RVOT is seen on the parasternal long-axis M mode.
 2. **RA collapse in ventricular systole.** RA collapse lasting over one-third of systole is specific for tamponade. RA collapse is generally more sensitive but less specific for tamponade than RV collapse.
 3. **Inspiratory changes of transmitral and transtricuspid flow.** An inspiratory decrease of left-sided transmitral flow by > 25%, or an inspiratory increase of right-sided transtricuspid flow, during *normal breathing*, suggests tamponade (this is equivalent to the pulsus paradoxus). This is the earliest echo sign of tamponade.
 4. **IVC dilatation with poor inspiratory collapse.** IVC abnormality has a sensitivity of 97% and a specificity of 40% for tamponade. IVC is rarely normal in tamponade (the so-called low-pressure tamponade).

Findings on **hepatic venous doppler**: the flat Y descent on the RA tracing corresponds to a *flat D wave* on the hepatic venous Doppler. This contrasts with constriction, where both S and D are prominent. Inspiratory rise of these waves may be seen in both conditions.

5. Other findings:

- A rapid change in the effusion size suggests a threatened tamponade.
- An abnormal septal motion may be seen as a result of ventricular interdependence.
- A swinging heart, i.e., a heart that changes position in a phasic manner, may be seen with a large effusion and corresponds to the electrical alternans seen on ECG. It does not necessarily imply tamponade.
- Strands in the pericardial fluid imply inflammation or bleeding and can be seen with most effusions, except transudative effusions. *TEE, CT, or MRI may be performed when a loculated effusion with a regional tamponade is suspected.*

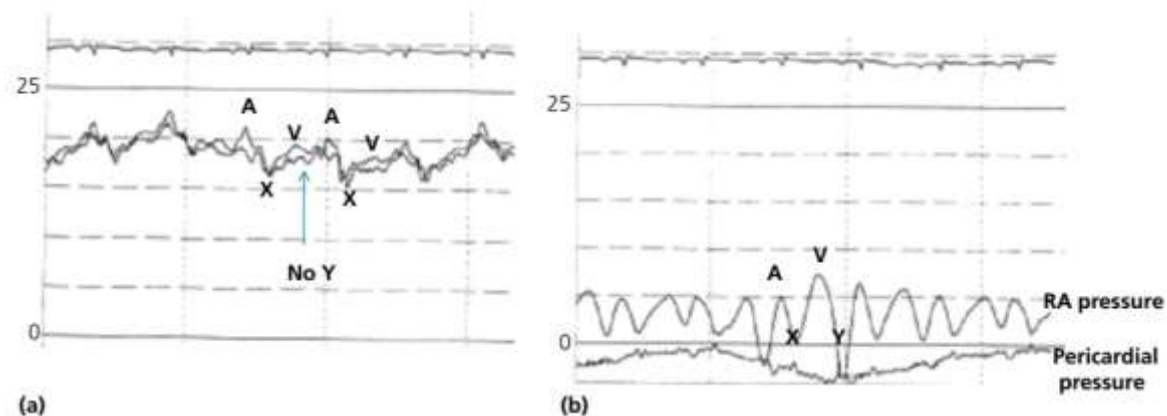


Figure 21-4: (a) Simultaneous pericardial and RA pressures are recorded in tamponade, before pericardiocentesis. The RA and pericardial pressures are elevated and equalized (~20mmHg); this defines tamponade. The two tracings are actually superimposed. Furthermore, X descent is seen, but Y descent is flat (mnemonic: Flat Y Tamponade=FYT). V wave almost continues straight into A wave. **(b)** Post-pericardiocentesis, pericardial pressure becomes normal (negative pressure ≤ 0 mmHg). RA pressure is normal with clear V wave and Y descent. Had the pericardial pressure or RA pressure not normalized, and had these pressures remained equal, effusive–constrictive pericarditis would have been suggested. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.



Figure 21-5: Pulsus paradoxus. Note the drop of systolic and pulse pressure during normal inspiration (arrows). The arterial waveform also becomes narrower. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

N.B:

Right heart catheterization may be performed before and particularly after pericardiocentesis to document the hemodynamic improvement.

Before drainage, pericardial pressure is elevated (> 0 mmHg) and equal to the RA pressure.

After drainage, the pericardial pressure (to ≤ 0 mmHg) and the RA pressure must be normalized. *The lack of full hemodynamic improvement suggests effusive–constrictive pericarditis.*

Treatment of tamponade:

Tamponade is initially temporized with fluid resuscitation. Avoid excessive fluid resuscitation, as excessive fluid administration may sometimes increase the right-sided volume, which further stretches the already distended pericardium and elevates its pressure, leading to a full-blown tamponade picture. That is why fluids are helpful in hypovolemic patients with tamponade but may harm euvoletic or hypervolemic patients.

Pericardiocentesis is urgently indicated, and the catheter is allowed to drain for ~ 3 days. Pericardiocentesis is often a definitive treatment of idiopathic effusions and late postoperative effusions, and at least a temporary treatment of malignant effusions.

A pericardial window is particularly useful for recurrences or loculated effusions.

| Table 21-8: ESC Recommendations for the management of pericardial effusion: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>In a patient with clinical suspicion of cardiac tamponade, echocardiography is recommended as the first imaging technique to evaluate the size, location and degree of hemodynamic impact of the pericardial effusion.</i> | I | C |
| <i>Urgent pericardiocentesis or cardiac surgery is recommended to treat cardiac tamponade.</i> | I | C |
| <i>A judicious clinical evaluation including echocardiographic findings is recommended to guide the timing of pericardiocentesis</i> | I | C |
| <i>Vasodilators and diuretics (preload reduction) are not recommended in the presence of cardiac tamponade.</i> | III | C |

Special circumstances:

- **Causes of absent pulsus paradoxus:**

1. Patients with **cor pulmonale** and patients with **ESRD and underlying left heart failure**:

While it is easy to induce tamponade in case of hypovolemia, it is difficult to induce tamponade physiology in patients with severely increased right-sided or left-sided diastolic pressure.

The lack of biventricular compression (and therefore lack of interdependence) and the lack of respiratory variation in ventricular output explain the lack of pulsus paradoxus.

2. **ASD**: where the increase in right-sided flow during inspiration is balanced by an increase in right-to-left shunt or reduction in left-to-right shunt, leading to less ventricular interdependence.

3. **Local tamponade** (e.g., localized compression of one ventricle or atrium by a clot after cardiac surgery, leading to a localized increase in pressure).

4. **AI**: where the diastolic regurgitant flow damps down respiratory fluctuations of flow.

5. **AF**: pulsus paradoxus is difficult to detect in case of an irregular rhythm.

- **Regional tamponade:**

This occurs when only one cardiac chamber, a pulmonary vein, or SVC or IVC is compressed by a loculated effusion (e.g. anterior loculation compressing RV or RA, posterior loculation compressing LV or LA).

Since there is no uniform compression of the four chambers, there is no equalization of diastolic pressures and no ventricular interdependence/pulsus paradoxus. There is increased pressure of the compressed chamber, e.g., increased RA pressure or PCWP, and hypotension, which in the right context suggest tamponade (e.g., after cardiac surgery). However, loculation can also produce classic tamponade, presumably by tightening the uninvolved pericardium.

TEE or cardiac CT or MRI should be performed when a regional tamponade is suspected.

- **Other causes of pulsus paradoxus and RV–LV respiratory discordance:**

Because of large intrathoracic pressure swings, COPD, asthma, morbid obesity, or positive-pressure ventilation may lead to discordance in RV and LV filling and pulsus paradoxus.

Constrictive Pericarditis

Constrictive pericarditis is due to pericardial scarring that takes years to develop, but in some instances it only takes a few months. The pericardium becomes a stiff “shell” that surrounds the right and left cardiac chambers and impairs their filling, leading to ***signs of right heart failure*** and ***symptoms of left heart failure***.

A transient constrictive physiology without pericardial scarring may be seen after any pericardial inflammation (such as 9% of acute idiopathic pericarditis).

| Table 21-9: Definitions and therapy of main constrictive pericardial syndromes | | |
|--|--|--|
| Syndrome | Definition | Therapy |
| <i>Transient constriction</i> (D.D. permanent constrictive pericarditis, restrictive CMP) | <i>Reversible pattern of constriction following spontaneous recovery or medical therapy.</i> | <i>2-3 months of empiric anti inflammatory medical therapy</i> |
| <i>Effusive-constrictive pericarditis</i> (D.D. cardiac tamponade, constrictive pericarditis). | <i>Failure of the right atrial pressure to fall by 50% <u>or</u> to a level below 10 mmHg after pericardiocentesis. May be diagnosed also by non invasive imaging.</i> | <i>Pericardiocentesis followed by medical therapy. Surgery for persistent cases.</i> |
| <i>Chronic constriction</i> (D.D. transient constriction, restrictive CMP). | <i>Persistent constriction after 3–6 months.</i> | <i>Pericardiectomy, medical therapy for advanced cases or high risk of</i> |

| | | |
|--|--|--|
| | | <i>surgery or mixed forms with myocardial involvement.</i> |
|--|--|--|

Causes:

- **The three most common causes are:**

- Idiopathic.
- Post-cardiac surgery: may appear as early as 2 weeks or as late as 25 years after cardiac surgery, the majority of cases appearing 3–24 months postoperatively. The constrictive process has an incidence of ~0.1% and may be related to the post-pericardiotomy syndrome. Constrictive pericarditis occurring within 2 months postoperatively warrants medical therapy with anti-inflammatory agents, as this early process is often an inflammatory, transient constrictive process with limited fibrosis.
- Post-mediastinal irradiation: typically develops years after radiation therapy (range 1–40 years).

- **Other less common causes:** Autoimmune (esp. Rheumatoid Arthritis), Post-infectious, Traumatic, Malignant.

Pathophysiology and hemodynamics:

- **During inspiration:**

- **In the absence of constriction**, there is an inspiratory decrease in PV, SVC and the intracardiac chambers pressure. Note that, IVC is affected by intrabdominal not intrathoracic pressures.
- **In constriction**, the negative pressure is transmitted to PV and SVC but not to the intracardiac chambers (due to pericardial obstruction) or the IVC.

This reduces blood flow between PV and LA, and thus between LA and LV (**reduced transmitral E velocity**).

Owing to ventricular interdependence, the reduced LV volume “sucks” the ventricular septum to the left. This increases RV volume, which “sucks” blood from RA (**increased transtricuspid E velocity**).

This explains the **ventricular systolic discordance** (RV systolic pressure increases whereas LV systolic pressure decreases during inspiration).

Since RV-to-RA sucking is increased with inspiration in early diastole and early systole, this “sucks” flow from the IVC and increases IVC-to-RA flow (**increased hepatic forward flow**).

Constriction prevents a decrease in RA pressure. Thus, the flow between SVC and RA decreases with inspiration, which ultimately leads to increased JVP with inspiration (**Kussmaul’s sign**).

Thus, **SVC and IVC pressures and flow patterns are divergent in constrictive pericarditis**.

- **The stiff pericardial shell results in three effects:**

1. Early during diastole, the pressures of all four cardiac chambers increase enough to equalize with the pressure exerted by the stretched “shell”, i.e., **a high pressure** of 15–25mmHg.
2. The shell prevents the transmission of intrathoracic pressure to the cardiac chambers (dissociation between intracardiac and intrathoracic pressures).
3. Both LV and RV are constricted within this shell, so that a change in volume of one chamber reflects upon the other (**ventricular interdependence**) ⁽¹⁾.

These three effects explain the following pathophysiology:

- *Diastolic pressure of all four cardiac chambers, diastolic PA pressure, and diastolic PCWP (~mean PCWP) all become high and equal to the pressure of the stretched pericardium (**high equalization of diastolic pressures**). Thus, mean RA pressure=mean PCWP and RVEDP=diastolic PA pressure=LVEDP.*
- **Ventricular dip–plateau pattern** and deep atrial X and Y descents (high RA pressure with M or W shape).

(1) While ventricular interdependence is present in both constriction and tamponade, a different mechanism is incriminated in each case: during inspiration, RV “pushes” LV in tamponade, whereas RV is “sucked” by LV in constrictive pericarditis.

As opposed to constrictive pericarditis, LV flow is reduced in tamponade because of RV compression, not because of a lack of transmission of the negative intrathoracic pressure to the LV. In addition, because of the uniform pericardial fluid, the constraint is more uniform across both the LV and the RV in tamponade. Thus, ventricular interdependence is more prominent in tamponade and leads to pulsus paradoxus, which is only present in one-third of cases of constriction.

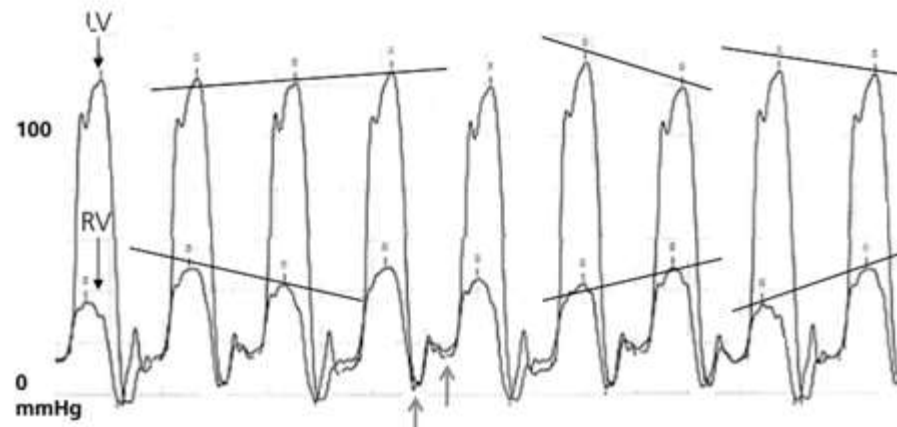


Figure 21-6: Simultaneous RV–LV pressure recording. This recording is the most important recording in assessing the presence of constrictive pericarditis. It shows the following:

1. Diastolic dip–plateau pattern of RV and LV tracings (dip=lower vertical gray arrow, plateau=upper vertical gray arrow).

It is not specific for constrictive pericarditis and, similarly to the deep X and deep Y on RA tracing, may be seen in decompensated systolic or diastolic ventricular failure with severe loss of compliance, including restrictive cardiomyopathy.

2. Equalization of end-diastolic pressures of RV and LV, mainly seen in inspiration (LV pressure>RV pressure at other times). Equalization of RV and LV end-diastolic pressures may be seen in RV failure as well, except that RV supersedes LV pressures at times.

3. While (1) and (2) correspond to the analysis of diastolic RV and LV pressures, the third feature corresponds to the analysis of systolic RV and LV pressures. **Discordance of peaks**, wherein the systolic peaks of RV and LV move in opposite directions, is very specific for constrictive pericarditis. This contrasts with restrictive cardiomyopathy or decompensated ventricular failure, wherein the peaks are concordant. There is discordance on this recording, as RV peak increases when LV peak decreases. The two *black lines* illustrate this concept. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

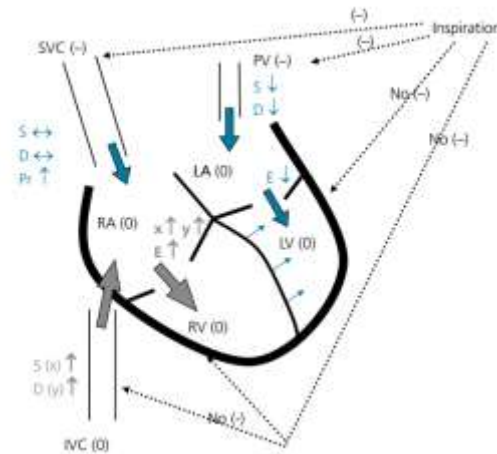


Figure 21-7: Sequence of events occurring during inspiration in constrictive pericarditis. (-) sign adjacent to a structure signifies there is transmission of the negative intrathoracic pressure to this structure, whereas (0) corresponds to the lack of transmission of the intrathoracic pressure to this structure. Gray block arrows signify increased flow between two chambers, while the blue block arrows signify reduced flow between two chambers. \leftrightarrow indicates lack of change. D, diastolic flow wave of IVC, SVC, and PV on Doppler, corresponds to Y descent; E, mitral inflow Doppler wave; S, systolic flow wave of IVC, SVC, and PV on Doppler, corresponds to X descent; Pr, pressure change that ultimately occurs in the SVC; PV, pulmonary veins. **D on echo is Y on pressure tracing, S is X (DY--SX).** Source: Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Diagnosis:

• Physical exam:

- *Signs of right heart failure*, sometimes isolated right heart failure. Constrictive pericarditis should always be considered in the differential diagnosis of isolated right heart failure:
 - Kussmaul's sign (i.e increased JVP with inspiration), Deep X and Y descents on JVP exam
 - Peripheral edema

- Ascites, hepatic congestion with jaundice (differentiate from cirrhosis by the elevated JVP and the hepatomegaly, vs. atrophic liver in cirrhosis).
- *Symptoms of elevated LA pressure* (dyspnea, orthopnea). Similar to tamponade, dyspnea occurs but pulmonary edema and hypoxemia do not usually occur because of the low volume reaching the left heart.
- *Low-output signs* (fatigue).
- *Pulsus paradoxus* in one-third of patients. Pulsus paradoxus is more common in tamponade than constriction, because of the more potent and uniform compression of both ventricles in tamponade (more extreme RV–LV discordance).
- Pericardial knock may be heard in diastole (sounds like a high-pitched S3).
- **ECG: almost always abnormal:** low QRS voltage (very commonly), and non-specific T-wave abnormalities (flat, inverted).
- **BNP:** In restrictive cardiomyopathy, BNP is always > 200 pg/ml, whereas in idiopathic constrictive pericarditis, it is < 200 pg/ml. BNP may be > 200 pg/ml in other forms of constrictive pericarditis (e.g., post-radiation). *Severe right HF with a normal BNP suggests constrictive pericarditis.*
- **Pericardial thickness:**
Pericardial thickness is usually increased (≥ 3 mm) in constrictive pericarditis and may be assessed by echo, CT or MRI. However, 18% of patients with constrictive pericarditis have normal pericardial thickness, and those patients are as likely as patients with a thickened pericardium to benefit from pericardiectomy.
A thickened pericardium with severe late gadolinium hyperenhancement of the pericardium itself suggests a reversible, inflammatory constrictive process.

Transient Constrictive Pericarditis:

- Up to 17% of patients with constrictive pericarditis may have a transient (reversible) constrictive pericarditis.
- This may be seen with idiopathic, post-surgical, traumatic, infectious, or collagen vascular disease. In this case, inflammation and edema lead to pericardial thickening and stiffening without fibrosis.

- Constrictive physiology resolves with observation and anti-inflammatory therapy within 6 months. NSAIDs, steroids, and colchicine have been used.
- The following markers have been shown to identify a reversible (vs. persistent) constrictive pericarditis:
 - Elevated markers of inflammation: CRP > 2.1 mg/dl, ESR > 41 mm/h.
 - On cardiac MRI; thick (≥ 3 mm) late gadolinium hyperenhancement of the pericardium. The normal pericardium and the fibrotic pericardium are poorly vascularized, and thus do not enhance with gadolinium; the fibrotic pericardium may mildly enhance. Conversely, severe gadolinium enhancement implies a predominantly inflamed, hyperemic rather than fibrotic pericardium.

N.B: Radiation-induced constrictive pericarditis cannot be transient.

Treatment:

Constrictive pericarditis (except transient form) is treated with pericardiectomy. Complete pericardiectomy consists of removing the pericardium from phrenic nerve to phrenic nerve and removing the diaphragmatic pericardium.

- The perioperative mortality is 6%, and varies with the etiology (~3% for idiopathic, ~20% for radiation-induced constrictive pericarditis).
- As a result of longstanding underfilling, LV myocardial atrophy occurs in patients with longstanding constrictive pericarditis. The sudden “flooding” of the LV that occurs postoperatively may lead to a transient LV systolic dysfunction with pulmonary edema and a low output syndrome, responsible for some of the early fatalities. In survivors, LV systolic function improves with time.
- Longterm survival is excellent for idiopathic constriction, good for postoperative constriction, and poor for radiation-induced (7-year survival is 88% vs. 66% vs. 27%, respectively).
- Predictors of poor longterm outcomes: NYHA class IV, age > 55, and especially radiation etiology.
- Echocardiographic normalization of diastolic filling pattern occurs slowly over several months and is seen in ~40% of patients at 3 months and 60% at 6 months.
- Symptomatic improvement is seen in ~80% of survivors. Patients with a longer duration of symptoms are more likely to have residual diastolic dysfunction and symptoms at later follow-up. This is due to:

Extension of the fibrotic process to the myocardium in longstanding constriction.

Inability to fully resect the pericardium in patients with extensive scarring (residual constriction).

| Table 21-10: ESC Recommendations for the Management of constrictive pericarditis: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>In all patients with suspected constrictive, all of the following is indicated:</i> | I | C |
| ○ <i>Transthoracic echocardiography</i> | | |
| ○ <i>Chest X-ray (frontal and lateral views) with adequate technical characteristics</i> | | |
| ○ <i>CT and/or CMR are indicated as second-level imaging techniques to assess calcifications (CT), pericardial thickness, degree and extension of pericardial involvement.</i> | | |
| <i>Cardiac catheterization is indicated when non-invasive diagnostic methods do not provide a definite diagnosis of constriction.</i> | I | C |
| Treatment: | | |
| <i>The mainstay of treatment of chronic permanent constriction is pericardiectomy.</i> | I | C |
| <i>Medical therapy of specific pericarditis (i.e. tuberculous pericarditis) is recommended to prevent the progression of constriction.</i> | I | C |
| <i>Empiric anti-inflammatory therapy may be considered in cases with transient or new diagnosis of constriction with concomitant evidence of pericardial inflammation (i.e. CRP elevation or pericardial enhancement on CT/CMR)</i> | IIb | C |

Effusive–constrictive pericarditis:

- Some patients have a pericardial effusion with the hemodynamics of tamponade, i.e., pulsus paradoxus with elevated and equalized right- and left-sided filling pressures. However, upon drainage of the pericardial fluid, the hemodynamic compromise does not fully resolve. RV and LV diastolic pressures remain equalized, RA pressure remains elevated (RA pressure declines by < 50%), and the pericardial pressure declines but remains high. A flat RA Y descent (tamponade) may become deep (constriction) after drainage of the pericardial fluid.
- Effusive–constrictive pericarditis is an effusion that occurs on a background of constrictive pericarditis. In patients with a non-compliant pericardium, tamponade may occur with relatively little accumulation of fluid.
- Effusive–constrictive pericarditis may be seen with constrictive pericarditis of any origin, particularly idiopathic or radiation-induced constrictive pericarditis, and is usually seen early in the disease course.
- In fact, up to 24% of constrictive pericarditis cases and 7% of tamponade cases have an effusive–constrictive pathophysiology.
- When idiopathic, effusive–constrictive pericarditis is often an inflammatory constrictive pericarditis that is transient in 50% of the cases and resolves with anti-inflammatory therapy; this is not the case with radiation induced effusive–constrictive pericarditis.

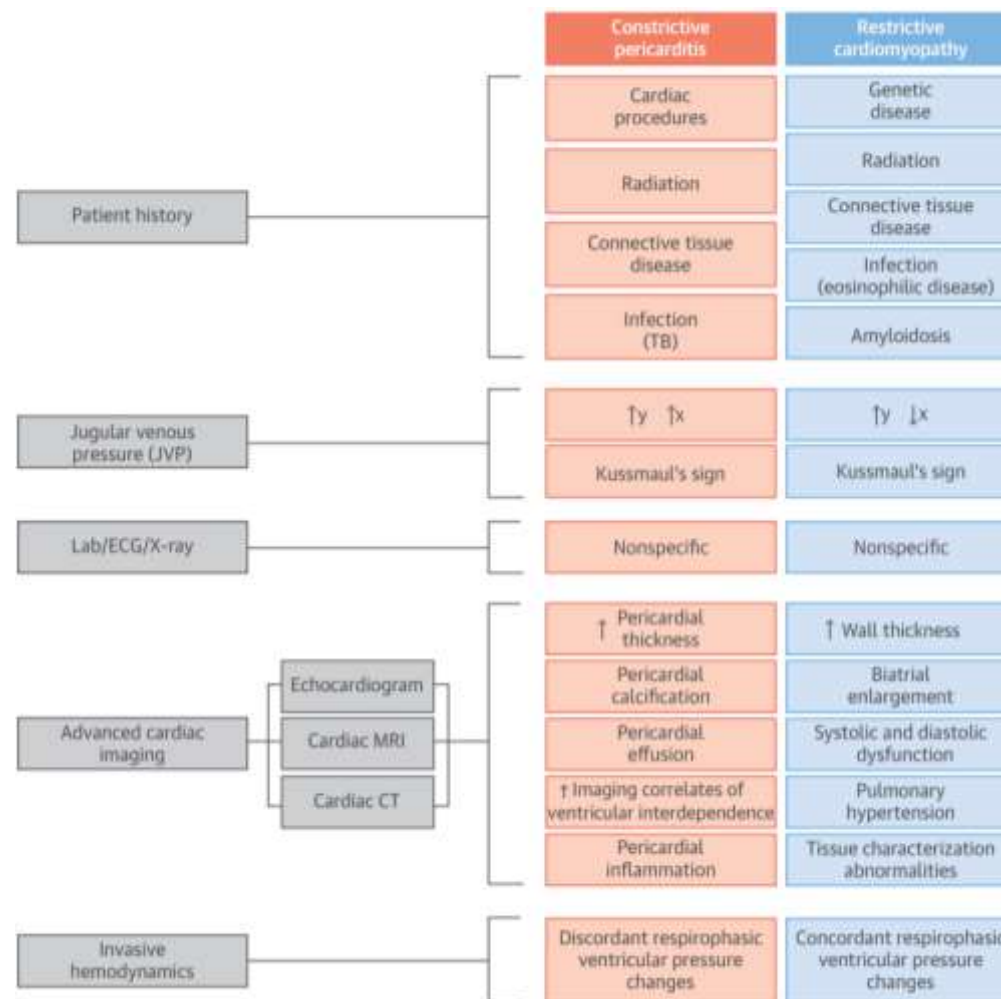


Figure 21-8: Differentiation of constriction and restriction requires a multifaceted approach inclusive of history, physical examination, laboratory testing, and multimodality imaging. Even with this toolset, hemodynamic catheterization remains necessary to provide definitive hemodynamic assessment for a subset of patients. **Source:** Geske JB, Anavekar NS, Nishimura RA, et al. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. Journal of the American College of Cardiology. 2016 Nov 29;68(21):2329-47.

Table 21-11: Comparison between Constrictive Pericarditis and Restrictive Cardiomyopathy:

| Diagnostic evaluation | Constrictive pericarditis | Restrictive cardiomyopathy |
|--|--|--|
| Physical findings | <i>Kussmaul sign, Pericardial knock</i> | <i>Regurgitant murmur, Kussmaul sign may be present, S3 (advanced)</i> |
| ECG | <i>Low voltage, non specific ST/T changes, AF</i> | <i>Low voltages, pseudoinfarction, possible widening of QRS, left axis deviation, AF</i> |
| Chest x-ray | <i>Pericardial calcifications (1/3 of cases)</i> | <i>No pericardial calcifications</i> |
| Echocardiography: | | |
| Shared Features: | <ul style="list-style-type: none"> - E/A > 1.5 - E deceleration time < 160 ms - Ventricular size/systolic function: Normal - Atria: Dilated (More dilated in restrictive cardiomyopathy) - IVC: Dilated | |
| Difference features: | | |
| <ul style="list-style-type: none"> - Respiratory E variation (during normal respiration) - Medial annular E' velocity - Hepatic venous pattern - Hepatic venous flow respiratory variation | <ul style="list-style-type: none"> - > 25% - > 10 cm/s - $S > D$ - ↑ S and D with inspiration, ↓ S and D with partial reversal of flow in expiration - ↑ S and D with expiration | <ul style="list-style-type: none"> - < 25% - < 10 cm/s - $S < D$ - Minimal variation - Minimal variation - Reduced |

| | | |
|---|--|--|
| <ul style="list-style-type: none"> - Pulmonary venous flow Respiratory variation - Color M-mode mitral valve velocity of propagation (Vp) - Septal motion on M-mode and 2D - Posterior wall motion in diastole on M mode - Pulmonary hypertension - TR and MR | <ul style="list-style-type: none"> - Normal (> 55 cm/s) (implies normal diastolic recoil, like medial E') - Abnormal (septal bounce in diastole due to competitive filling of RV and LV) - <i>Dip</i>—plateau (after early expansion, posterior wall remains flat in diastole) - < 55 mmHg - Infrequent | <ul style="list-style-type: none"> - Normal - Normal - > 55 mmHg - Frequent, may be severe |
| CT/CMR | <i>Pericardial thickening > 3-4 mm, Pericardial calcifications (CT), Ventricular interdependence (real-time cine CMR).</i> | <i>Normal pericardial thickness (< 3.0 mm), Myocardial involvement (CMR).</i> |
| Cardiac Catheterization: | | |
| Shared Features: | <ol style="list-style-type: none"> 1. Elevated right- and left-sided filling pressures (elevated RA pressure and PCWP) 2. Ventricular dip–plateau pattern 3. Deep atrial X and Y descents with an atrial M morphology (V wave may be large with flattened X descent in restrictive cardiomyopathy or ventricular failure, particularly in severe TR) | |

| | | |
|--|---|--|
| <p>Difference Features:</p> <ul style="list-style-type: none"> - RV and LV pressures - Effect of inspiration on RA pressure - Effect of inspiration on RV & LV pressures - PCWP-LV gradient ¹⁾ - Systolic PA pressure | <ul style="list-style-type: none"> ○ Equalization of RV and LV end-diastolic pressures (RV = LV in inspiration, RV < LV in expiration) ○ No or minimal inspiratory decrease of RA pressure (X and Y become deeper and RA pressure may increase with inspiration) ○ During respiration, there is a discordant change of the systolic peaks of LV and RV (when RV pressure ↑, LV pressure ↓) ○ Early diastolic gradient between PCWP and LV varies with respiration > 5 mmHg. ○ < 55 mmHg | <ul style="list-style-type: none"> ○ LV diastolic pressure often > RV diastolic pressure by > 5 mmHg ○ Inspiratory decrease of RA pressure ○ During respiration, there is a concordant change of the systolic peaks of LV and RV ○ No significant change of PCWP–LV early diastolic gradient ○ > 55 mmHg |
|--|---|--|

(1) In constriction, the LV diastolic pressure varies minimally with respiration whereas the PCWP varies markedly, which explains the significant respiratory change of the early diastolic PCWP–LV gradient (lowest during inspiration).

In other disease states, the LV diastolic pressure changes as much as the PCWP with respiration, hence the lack of significant change of the PCWP–LV early diastolic gradient.

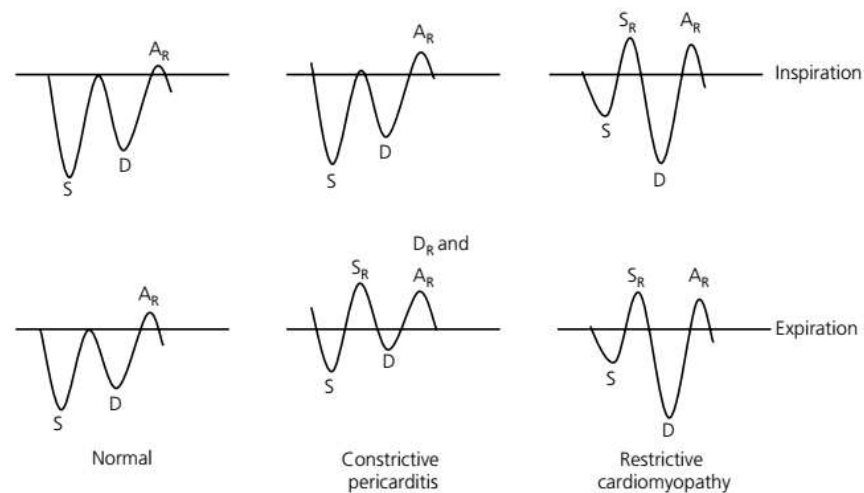


Figure 21-9: Respiratory variations of hepatic venous flow velocities. **S** flow corresponds to the X descent on RA and IVC pressure tracing, **D** flow corresponds to the Y descent ($S=X$, $D=Y$), and **A_r** flow corresponds to A wave. In **constrictive pericarditis**, S and D increase with inspiration (i.e., increase in X and Y descent); S and D decrease with expiration along with a terminal S reversal (S_R) and a terminal D reversal (D_R). Minimal respiratory variations are seen in normal individuals and in restrictive cardiomyopathy. In the latter case, there is a reduction of S velocity (= X descent) with terminal S reversal (= V wave), and an increase of D velocity (= Y descent) and A reversal. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Pericardial diseases in Specific circumstances:

▪ Tuberculous pericarditis:

Table 21-12: A stepwise protocol for the evaluation of suspected tuberculous pericarditis and pericardial effusion:

| | |
|-----------------|--|
| Stage 1: | - Chest radiograph may suggest pulmonary T.B in 30% of cases. |
|-----------------|--|

| | |
|---|---|
| <p>Initial non-invasive evaluation</p> | <ul style="list-style-type: none"> - Echocardiogram: Large pericardial effusion with frond-like projections, and thick "porridge-like" fluid is suggestive of an exudate but not specific for T.B. - CT scan and/or MRI of the chest: look for evidence of pericardial effusion and thickening (> 3 mm), and typical mediastinal and tracheobronchia lymphadenopathy (> 10 mm, hypodense centres, matting), with sparing of hilar lymph nodes. - Culture of sputum, gastric aspirate, and/or urine for <i>Mycobacterium tuberculosis</i> (<i>M. tuberculosis</i>) should be considered in all patients. - Scalene lymph node biopsy if pericaedial effusion is not accessible and lymphadenopathy present. - Tuberculin skin test is not helpful in adults regardless of the background prevalence of tuberculosis. - If pericardial fluid is not accessible, a diagnostic score of ≥ 6 based on the following criteria is highly suggestive of tuberculous pericarditis in people living in endemic areas: fever (1), night sweats (1), weight loss (2), globulin level > 40 g/L (3) and WBCs < $10 \times 10^9/L$ (3). |
| <p>Stage 2: Pericardiocentesis</p> | <ul style="list-style-type: none"> - Therapeutic pericardiocentesis is indicated in the presence of tamponade. - Diagnostic pericardiocentesis should be considered in all patients with suspected tuberculous pericarditis, and the following tests performed on the pericardial effusion <ol style="list-style-type: none"> 1. Direct inoculation of the pericardial fluid into double strength liquid Kirschner culture medium (or equivalent medium) and culture for <i>M. tuberculosis</i>. 2. Quantitative PCR testing for nucleic acids of <i>M. tuberculosis</i>. 3. Biochemical tests to distinguish between an exudate and transudate (fluid and serum protein, fluid and serum LDH) 4. White cell analysis and count, and cytology: a lymphocytic exudate favours tuberculous pericarditis. |

| | |
|---|---|
| | 5. <i>Indirect tests for tuberculous infection: interferon-gamma (IFN-γ), adenosine deaminase (ADA), or lysozyme assay.</i> |
| Stage 3: Pericardial biopsy | <ul style="list-style-type: none"> - “Therapeutic” biopsy: <i>as part of surgical drainage in patients with cardiac tamponade relapsing after pericardiocentesis or requiring open drainage of pericardial fluid for reasons such as repeated accumulation of pericardial fluid or failure to respond to empiric medical therapy.</i> - Diagnostic biopsy: <i>In areas where tuberculosis is endemic, a diagnostic biopsy is not required prior to commencing empiric antituberculosis treatment.</i> <i>In areas where tuberculosis is not endemic, a diagnostic biopsy is recommended in patients with > 3 weeks of illness and without aetiologic diagnosis having been reached by other tests.</i> |
| Stage 4: Empiric antituberculosis chemotherapy | <ul style="list-style-type: none"> - Tuberculosis endemic in the population: <i>trial of empiric antituberculosis chemotherapy is recommended for exudative pericardial effusion, after excluding other causes such as malignancy, uraemia, trauma, purulent pericarditis, and auto-immune diseases.</i> - Tuberculosis not endemic in the population: <i>when systematic investigation fails to yield a diagnosis of tuberculous pericarditis, there is no justification for starting antituberculosis treatment empirically.</i> |

Table 21-13: ESC Recommendations for the diagnosis and treatment of tuberculous pericarditis and effusion:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Diagnostic pericardiocentesis should be considered in all patients with suspected tuberculous pericarditis.</i> | IIa | C |
| <i>Intrapericardial urokinase may be considered to reduce the risk of constriction in tuberculous effusive pericarditis</i> | IIb | C |

| | | |
|--|------------|----------|
| <i>In patients living in non-endemic areas, empiric antituberculosis treatment is not recommended when systematic investigation fails to yield a diagnosis of tuberculous pericarditis</i> | III | C |
| <i>In patients living in endemic areas, empiric antituberculosis chemotherapy is recommended for exudative pericardial effusion, after excluding other causes</i> | I | C |
| <i>Adjunctive steroids may be considered in HIV-negative cases of TB pericarditis and avoided in HIV-associated TB pericarditis</i> | IIb | C |
| <i>Standard antituberculosis drugs for 6 months is recommended for the prevention of tuberculous pericardial constriction</i> | I | C |
| <i>Pericardiectomy is recommended if the patient's condition is not improving or is deteriorating after 4–8 weeks of antituberculosis therapy</i> | I | C |

▪ **Purulent pericarditis:**

| Table 21-14: ESC Recommendations for the management of purulent pericarditis: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Urgent pericardiocentesis is recommended for the diagnosis of purulent pericarditis</i> | I | C |
| <i>It is recommended that pericardial fluid be sent for bacterial, fungal and tuberculous studies and blood drawn for cultures</i> | I | C |
| <i>Effective pericardial drainage is recommended for purulent pericarditis</i> | I | C |
| <i>Administration of intravenous antibiotics is indicated to treat purulent pericarditis</i> | I | C |
| <i>Subxiphoid pericardiotomy and rinsing of the pericardial cavity should be considered</i> | IIa | C |
| <i>Intrapericardial thrombolysis should be considered</i> | IIa | C |
| <i>Pericardiectomy for dense adhesions, loculated or thick purulent effusion, recurrence of tamponade, persistent infection and progression to constriction should be considered</i> | IIa | C |

▪ **Pericarditis in renal failure:**

| Table 21-15: ESC Recommendations for the management of pericarditis in renal failure: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Dialysis should be considered in uraemic pericarditis</i> | IIa | C |
| <i>When patients with adequate dialysis develop pericarditis, intensifying dialysis should be considered</i> | IIa | C |
| <i>Pericardial aspiration and/or drainage may be considered in non-responsive patients with dialysis</i> | IIb | C |
| <i>NSAIDs and corticosteroids (systemic or intrapericardial) may be considered when intensive dialysis is ineffective</i> | IIb | C |
| <i>Colchicine is contraindicated in patients with pericarditis and severe renal impairment.</i> | III | C |

▪ **Traumatic pericardial effusion and hemopericardium:**

| Table 21-16: ESC Recommendations for the management of traumatic pericardial effusion and haemopericardium in aortic dissection: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Urgent imaging technique (transthoracic echocardiogram or CT) is indicated in patients with a history of chest trauma and systemic arterial hypotension</i> | I | B |
| <i>Immediate thoracotomy is indicated in cardiac tamponade due to penetrating trauma to the heart and chest</i> | I | B |

| | | |
|--|------------|----------|
| <i>In the setting of aortic dissection with hemopericardium, controlled pericardial drainage of very small amounts of the hemopericardium should be considered to temporarily stabilize the patient in order to maintain blood pressure at about 90 mmHg</i> | Ila | C |
| <i>Pericardiocentesis as a bridge to thoracotomy may be considered in cardiac tamponade due to penetrating trauma to the heart and chest</i> | Ilb | B |

▪ **Post-cardiac injury syndromes (PCIS):**

| Table 21-17: ESC Recommendations for the management and prevention of post-cardiac injury syndromes: | | |
|---|--------------|--------------|
| Recommendation | Class | Level |
| <i>Anti-inflammatory therapy is recommended in patients with PCIS to hasten symptom remission and reduce recurrences</i> | I | B |
| <i>Aspirin is recommended as a first choice for anti-inflammatory therapy of post-myocardial infarction pericarditis and those patients already on antiplatelet therapies</i> | I | C |
| <i>Colchicine added to aspirin or NSAIDs should be considered for the therapy of PCIS, as in acute pericarditis</i> | Ila | B |
| <i>Colchicine should be considered after cardiac surgery using weight-adjusted doses (i.e. 0.5 mg once for patients \leq 70 kg and 0.5 mg twice daily for patients $>$ 70 kg) and without a loading dose for the prevention of PPS if there are no contraindications and it is tolerated. Preventive administration of colchicine is recommended for 1 month</i> | Ila | A |
| <i>Careful follow-up after PCIS should be considered to exclude possible evolution towards constrictive pericarditis with echocardiography every 6–12 months according to clinical features and symptoms</i> | Ila | C |

▪ **Radiation pericarditis:**

Most cases are secondary to radiation therapy for *Hodgkin lymphoma or breast or lung cancer*, and serious radiation-induced pericardial disease was most often due to radiation therapy of Hodgkin lymphoma.

Table 21-18: ESC Recommendations for prevention and management of radiation pericarditis:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Radiation therapy methods that reduce both the volume and the dose of cardiac irradiation are recommended whenever possible</i> | I | C |
| <i>Pericardiectomy should be considered for radiation-induced constrictive pericarditis, but with a worse outcome than when performed for constrictive pericarditis of other causes, because of co-existing myopathy</i> | IIa | B |

▪ **Chylopericardium:**

Chylopericardium is a pericardial effusion composed of chyle, the normal content of the lymphatic vessels. It is a rare disorder that may be primary or, more often, secondary to injury to the thoracic duct, which carries chyle from the intestinal tract to the blood at the junction of the left internal jugular and left subclavian veins. It is often associated to chylothorax. Cardiac complications are cardiac tamponade, acute pericarditis, and chronic constriction.

Table 21-19: ESC Recommendations for diagnosis and management of chylopericardium:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Chylopericardium is diagnosed in the presence of a milky opalescent pericardial effusion, with a triglyceride level > 500 mg/dl, cholesterol : triglyceride ratio < 1, negative cultures and lymphocyte predominance (lymphocyte count between a few hundred to several thousand per millilitre)</i> | I | C |
| <i>Pericardial drainage and parenteral nutrition should be considered in symptomatic or large uncontrolled effusion due to chylopericardium.</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>Surgical therapy should be considered for chylopericardium if conservative therapy does not reduce pericardial drainage and the course of the thoracic duct is identified</i> | IIa | C |
| <i>Therapy with octreotide (100 mg s.c. × 3/day for 2 weeks) may be considered for chylopericardium (the mechanism of action is presumed to be a reduction in chyle production)</i> | IIb | C |

▪ **Pericardial involvement in neoplastic disease**

Primary tumors of the pericardium, either benign (lipomas and fibromas) or malignant (mesotheliomas, angiosarcomas, fibrosarcomas), are very rare. Mesothelioma, the most malignant tumor, is almost always incurable.

The most common neoplastic pericardial involvement is due to secondary malignant tumors (especially lung cancer, breast cancer, lymphoma, and leukemias).

| Table 21-20: ESC Recommendations for management of neoplastic pericardial diseases: | | |
|--|---------------------|---------------------|
| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
| <i>Pericardiocentesis is recommended for cardiac tamponade to relieve symptoms and establish the diagnosis of malignant pericardial effusion.</i> | I | B |
| <i>Cytological analyses of pericardial fluid are recommended for the confirmation of malignant pericardial disease</i> | I | B |
| <i>Pericardial or epicardial biopsy should be considered for the confirmation of malignant pericardial disease.</i> | IIa | B |
| <i>Tumour marker testing should be considered for distinguishing malignant from benign effusions in pericardial fluid.</i> | IIa | B |
| <i>Systemic antineoplastic treatment is recommended in confirmed cases of neoplastic aetiology</i> | I | B |
| <i>Extended pericardial drainage is recommended in patients with suspected or definite neoplastic pericardial effusion in order to prevent effusion recurrence and provide intrapericardial therapy.</i> | I | B |

| | | |
|---|------------|----------|
| <i>Intrapericardial instillation of cytostatic/ sclerosing agents should be considered since it may prevent recurrences in patients with malignant pericardial effusion.</i> | Ila | B |
| <i>Intrapericardial cisplatin should be considered in pericardial involvement in the course of lung cancer and intrapericardial instillation of thiotepa should be considered in breast cancer pericardial metastases</i> | Ila | B |
| <i>Radiation therapy should be considered to control malignant pericardial effusion in patients with radiosensitive tumours such as lymphomas and leukaemias.</i> | Ila | B |
| <i>Pericardiotomy should be considered when pericardiocentesis cannot be performed</i> | Ila | B |
| <i>Percutaneous balloon pericardiotomy may be considered for the prevention of recurrences of neoplastic pericardial effusions</i> | Ilb | B |
| <i>Pericardial window creation via left minithoracotomy may be considered in the surgical treatment of malignant cardiac tamponade.</i> | Ilb | B |
| <i>Interventional techniques should consider seeding of neoplastic cells, patient prognosis and the overall quality of life of the patients.</i> | Ila | C |

▪ **Acute and recurrent pericarditis in children**

- Compared to adults, children often have a marked inflammatory clinical pattern, with more common fever, pleuropulmonary involvement, raised CRP, and less common ANA positively.
- NSAIDs remain the mainstay, at high doses. Most pediatricians avoid aspirin in children. Colchicine halved recurrences also in children. Corticosteroids use should be restricted in children even more than in adults, given their side effects (striae rubre and growth impairment).
- Anakinra (anti-IL1 receptor) is a new option for children, especially, if corticosteroids-dependant.
- Severe physical restriction is bothersome in children and may further worsen their quality of life and that of their family.

- Long-term prognosis in children is good; however, quality of life can be severely affected with repeated recurrences, glucocorticoid dependence and severe physical restriction.

| Table 21-21: ESC Recommendations for therapy of pericardial diseases in children: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>NSAIDs at high doses are recommended as first-line therapy for acute pericarditis in children until complete symptom resolution.</i> | I | C |
| <i>Colchicine should be considered as an adjunct to anti-inflammatory therapy for acute recurrent pericarditis in children: < 5 years= 0.5 mg/day; > 5 years= 1.0–1.5 mg/day in two to three divided doses</i> | IIa | C |
| <i>Anti-IL-1 drugs may be considered in children with recurrent pericarditis and especially when they are corticosteroid dependent.</i> | IIb | C |
| <i>Aspirin is not recommended in children due to the associated risk of Reye's syndrome and hepatotoxicity.</i> | III | C |
| <i>Corticosteroids are not recommended due to the severity of their side effects in growing children, unless there are specific indications such as autoimmune diseases.</i> | III | C |

References and suggested readings:

- Yehuda Adler, Philippe Charron, Massimo Imazio, et al., ESC Scientific Document Group, 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS), *European Heart Journal*, Volume 36, Issue 42, 7 November 2015, Pages 2921–2964

- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).
- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
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Section

VI

Congenital Heart Diseases

TO THE POINT

Chapter 22:

Congenital Heart Diseases

Summary of Cardiovascular Embryology:

The cardiovascular system is one of the first body systems to appear within the embryo. It is active by the beginning of the **fourth week** (when the placenta is unable to meet the requirements of the growing embryo).

Primitive heart tube formation:

Five dilations appear along the length of the tube, namely, **sinus venosus**, **primitive atrium**, **primitive ventricle**, **bulbus cordis**, and the **truncus arteriosus**.

These five dilations undergo **dextral looping** and develop into the adult structures of the heart:

1. Sinus venosus → Smooth part of right atrium (sinus venarum), coronary sinus and Oblique vein of left atrium.
2. Primitive atrium → Trabeculated part of both right and left atria.
3. Primitive ventricle → Trabeculated part of both right and left ventricles.
4. Bulbus cordis → Smooth part of right ventricle (conus arteriosus) and Smooth part of left ventricle (aortic vestibule).
5. Truncus arteriosus → Aorta and pulmonary trunk.

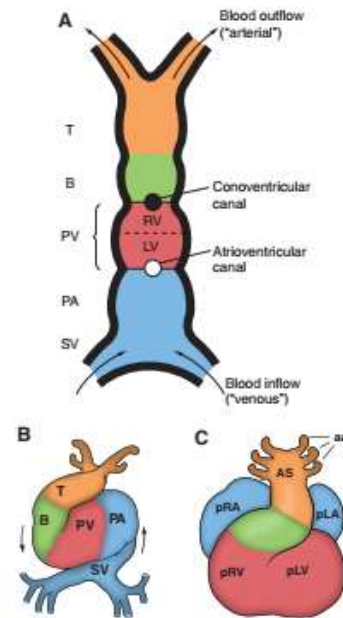


Figure 22-1: Schematic diagrams depict the primitive heart tube and its five dilations. (A) At 22 days: Note the location of the atrioventricular canal and conoventricular canal. Arrows show the direction of blood flow from the “venous” blood inflow at the sinus venosus to the “arterial” blood outflow at the truncus arteriosus. Note that “venous” blood inflow enters the left ventricle before it enters the right ventricle. **(B) At 26 days:** Note that the straight heart tube begins dextral looping (curved arrows). T= truncus arteriosus; B= bulbus cordis; PV= primitive ventricle; PA= primitive atrium; SV= sinus venosus. **(C) At 30–35 days:** Dextral looping is complete, and the four primitive heart chambers are apparent. Aa= aortic arches; AS= aortic sac; pRA= primitive right atrium; pRV= primitive right ventricle; pLA= primitive left atrium; pLV= primitive left ventricle. **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams and Wilkin.

▪ The atrial septum:

The crescent-shaped **septum primum** forms in the roof of the primitive atrium and grows toward the atrioventricular (AV) cushions in the AV canal. The **foramen primum** forms between the free edge of the septum primum and the AV cushions. The

foramen primum closes when the septum primum fuses with the AV cushions. The **foramen secundum** forms in the center of the septum primum. The crescent-shaped **septum secundum** forms to the right of the septum primum. The **foramen ovale** is the opening between the upper and lower limbs of the septum secundum. During embryonic life, blood is shunted from the right atrium to the left atrium via the foramen ovale.

Immediately after birth, functional closure of the foramen ovale is facilitated both by a **decrease in right atrial pressure** (due to occlusion of placental circulation) and by an **increase in left atrial pressure** (due to increased pulmonary venous return). Later in life, the septum primum and septum secundum anatomically fuse to complete the formation of the atrial septum.

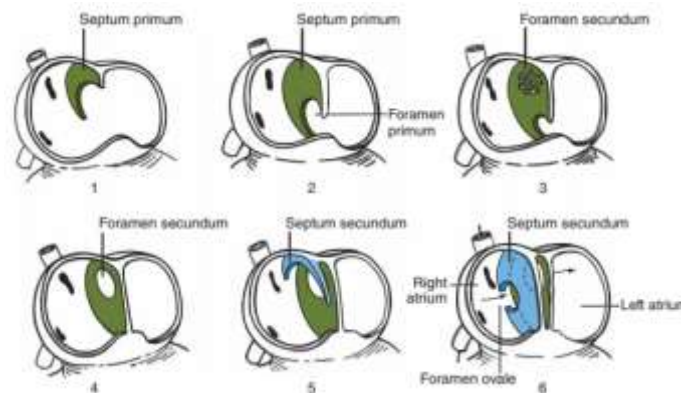
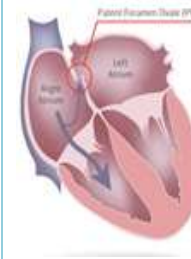


Figure 22-2: Formation of the atrial septum. The arrows in 6 indicate the direction of blood flow from the right atrium to the left atrium across the fully developed atrial septum. Septum primum= green, septum secundum= blue. **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams and Wilkin.

Table 22-1: Clinical considerations in Formation of Atrial septal defects:

Patent foramen ovale

Incomplete anatomic fusion of septum primum and septum secundum. It is present in approximately 25% of the population and is usually of no clinical importance.

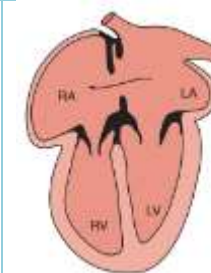


Premature closure of foramen ovale

Closure of the foramen ovale during prenatal life. It results in hypertrophy of the right side of the heart and underdevelopment of the left side of the heart.

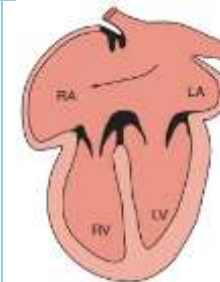
Ostium secundum defect:

Excessive resorption of septum primum, septum secundum, or both. This results in a condition in which there is an opening between the right and left atria. It is the most common clinically significant atrial septal defect (ASD).



Common atrium (cor triloculare biventriculare)

Complete failure of septum primum and septum secundum to develop. This results in a condition in which there is formation of only one atrium.



▪ **The atrioventricular (AV) septum:**

The **dorsal** and **ventral AV cushions** approach each other and fuse to form the AV septum. The AV septum partitions the AV canal into the right AV canal and left AV canal.

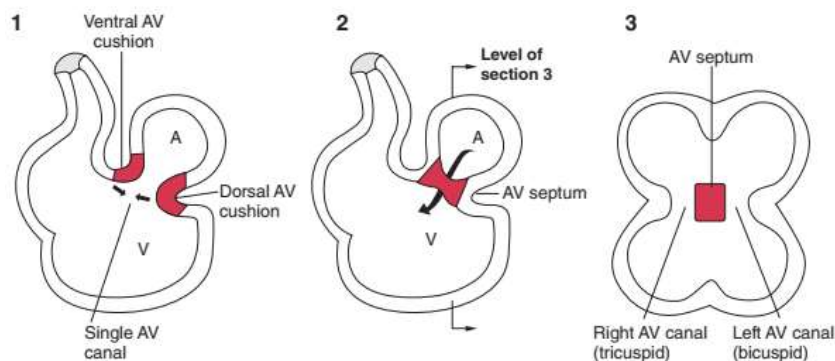


Figure 22-3: Formation of the atrioventricular (AV) septum. The AV septum partitions the atrioventricular canal. AV septum= red. **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams and Wilkin.

Table 22-2: Clinical considerations in Formation of Atrial septal defects:

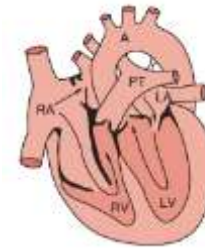
Common AV canal:

Failure of fusion of the dorsal and ventral AV cushions. It results in a condition in which the common AV canal fails to partition into the right and left AV canals. Consequently, the tricuspid and bicuspid valves are represented by one valve (common AV valve) common to both sides of the heart.



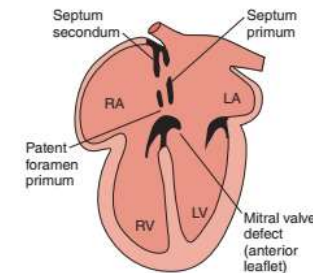
Ebstein anomaly:

Failure of the posterior and septal leaflets of the tricuspid valve to attach normally to the annulus fibrosus; instead they are displaced inferiorly into the right ventricle. It results in a division of the right ventricle into a large, upper, “atrialized” portion and a small, lower, functional portion. There is a reduced amount of blood available to the pulmonary trunk due to the small, functional portion of the right ventricle.



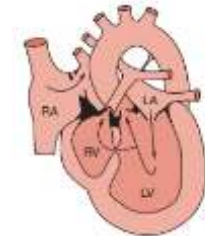
Ostium primum defect:

Failure of the AV septum to fuse with the septum primum. It results in a failure of the foramen primum to close (patent foramen primum) and is generally accompanied by an abnormal mitral valve.



Tricuspid atresia (hypoplastic right heart):

Insufficient amount of AV cushion tissue available for the formation of the tricuspid valve. It results in a complete agenesis of the tricuspid valve so that no communication between the right atrium and right ventricle exists.



▪ **Interventricular (IV) septum:**

The **muscular interventricular (IV) septum** develops in the midline on the floor of the primitive ventricle and grows toward the fused AV cushions. The **IV foramen** is located between the free edge of the muscular IV septum and the fused AV cushions. The

IV foramen is closed by the **membranous IV septum**. The membranous IV septum forms by the proliferation and fusion of tissue from three sources: the **right bulbar ridge**, **left bulbar ridge**, and **AV cushions**.

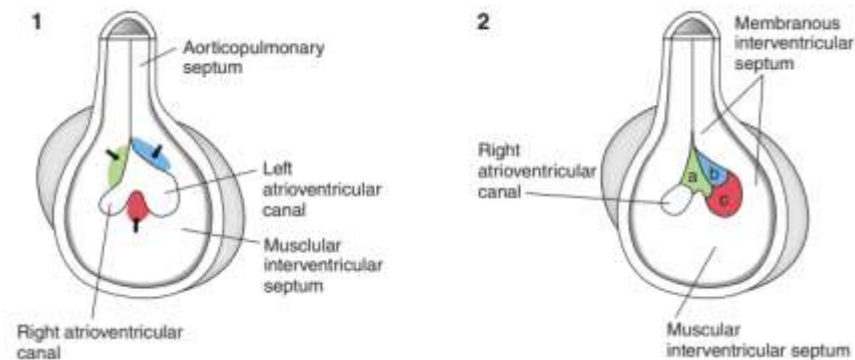


Figure 22-4: Formation of the interventricular (IV) septum. The IV septum partitions the primitive ventricle. The three sources of the membranous interventricular septum are indicated: a= right bulbar ridge (green); b= left bulbar ridge (blue); c= atrioventricular (AV) cushions (red). **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams and Wilkin.

Table 22-3: Clinical considerations in Formation of Interventricular septum:

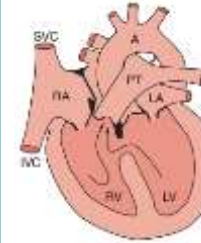
Muscular VSD:

Single or multiple perforations in the muscular IV septum



Membranous VSD:

Faulty fusion of the right bulbar ridge, left bulbar ridge, and AV cushions. It results in an opening between the right and left ventricles, which allows free flow of blood.



Common ventricle (cor triloculare biatriatum):

Failure of the membranous and muscular IV septa to form.



▪ **The Aorticopulmonary septum:**

Neural crest cells migrate from the hindbrain region through pharyngeal arches 3, 4, and 6 and invade both the **truncal ridges** and **bulbar ridges**. The truncal and bulbar ridges grow and twist around each other in a **spiral** fashion and fuse to form the aorticopulmonary (AP) septum. The AP septum divides the truncus arteriosus and bulbus cordis into the aorta and pulmonary trunk.

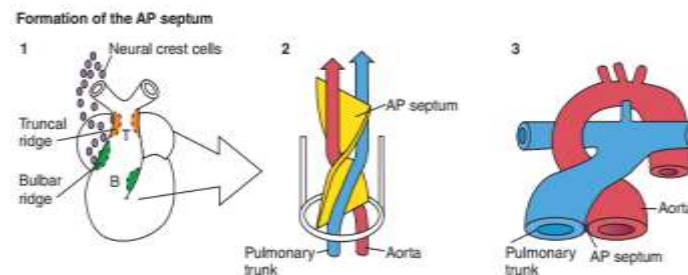
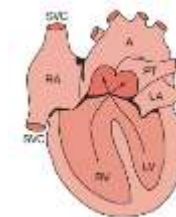


Figure 22-5: Formation of the aorticopulmonary (AP) septum. T= truncal ridges (orange), B= bulbar ridges (green). **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams and Wilkin.

Table 22-4: Clinical considerations in Formation of the aorticopulmonary (AP) septum:

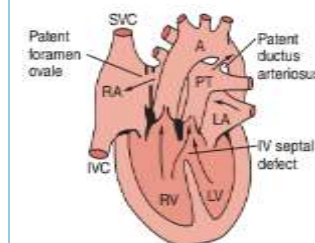
Truncus Arteriosus

Only partial development of the AP septum occurs. Truncus Arteriosus results in a condition in which one large vessel leaves the heart and receives blood from both the right and left ventricles.



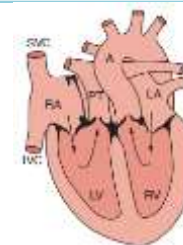
d-TGA:

Non-spiral development of the AP septum occurs. d-Transposition results in a condition in which the aorta arises abnormally from the right ventricle and the pulmonary trunk arises abnormally from the left ventricle. It is incompatible with life unless an accompanying shunt exists, like a VSD, patent foramen ovale, or patent ductus arteriosus.



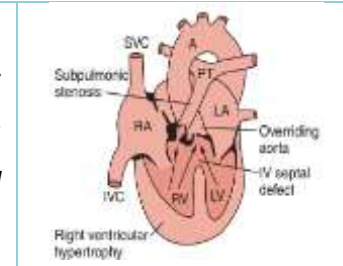
Congenitally corrected-TGA (cc-TGA):

Transposition of the aorta and pulmonary trunk along with “inverted” ventricles such that the anatomical right ventricle lies on the left side and the anatomical left ventricle lies on the right side. These two major deviations offset one another such that the blood flow pattern is normal.



Tetralogy of Fallot:

Skewed development of the AP septum occurs. TOF results in a condition in which the pulmonary trunk exhibits a small diameter and the aorta exhibits a large diameter. TOF is characterized by four classic malformations: pulmonary stenosis, right ventricular hypertrophy, overriding aorta, and ventricular septal defect.



▪ Development of the arterial system:

In the head and neck region, the arterial pattern develops mainly from six pairs of arteries (called **aortic arches**) that course through the pharyngeal arches. The aortic arch arteries undergo a complex remodeling process that results in the adult arterial pattern. In the rest of the body, the arterial patterns develop mainly from the **right and left dorsal aortae**. The right and left dorsal aortae fuse to form the **dorsal aorta**, which then sprouts **posterolateral arteries**, **lateral arteries**, and **ventral arteries (vitelline and umbilical)**.

Most anomalies of the great arteries occur as a result of the persistence of parts of the aortic arch system that normally regress and the regression of parts that should normally persist.

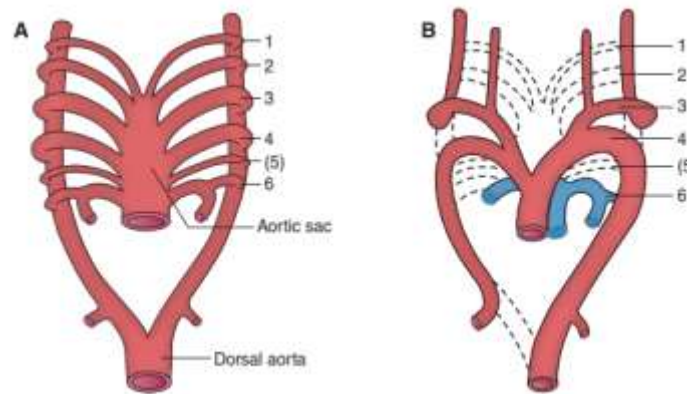

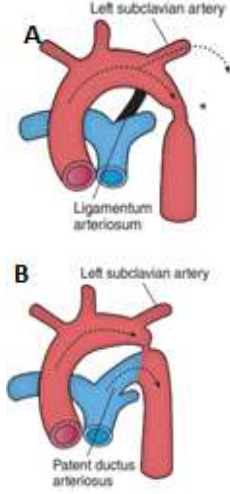


Figure 22-6: Development of the arterial system. A, B. Development and fate of the aortic arches during the remodeling process. Note the portions of the aortic arches that degenerate during the remodeling process (*dashed lines*). **Source:** Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams And Wilkin.

Table 22-5: Correspondence of embryonic arteries to their derivative adult counterparts:

| Embryonic | Adult |
|---------------|--|
| Aortic arch 1 | <i>Maxillary artery</i> |
| Aortic arch 2 | <i>Stapedial artery</i> |
| Aortic arch 3 | <i>CCA and ICA</i> |
| Aortic arch 4 | <i>Right subclavian artery</i> <i>Arch of the aorta</i> |
| Aortic arch 5 | <i>Disappears</i> |
| Aortic arch 6 | <i>Right and left pulmonary arteries</i> <i>Ductus arteriosus</i> |

| Table 22-6: Clinical considerations in Formation of arterial system: | | |
|--|--|--------------|
| Disease | Cause | Illustration |
| Aberrant right subclavian artery | <i>Occurs when right 4th aortic arch and the right dorsal aorta cranial to the 7th intersegmental artery abnormally regress. As development continues, the right subclavian artery lies on the left side just inferior to the left subclavian artery. The right subclavian artery must therefore cross the midline posterior to the trachea and esophagus to supply the right arm. This anomaly may constrict the trachea or esophagus. However, it is generally not clinically significant.</i> | |
| Double aortic arch | <i>Occurs when an abnormal right aortic arch develops in addition to a left aortic arch due to persistence of the distal portion of the right dorsal aorta. This forms a vascular ring around the trachea and esophagus, which causes difficulties in breathing and swallowing.</i> | |
| Right aortic arch | <i>Occurs when the entire right dorsal aorta abnormally persists and part of the left dorsal aorta regresses. The right aortic arch may pass anterior or posterior (retroesophageal right arch) to the esophagus and trachea. A retroesophageal right arch may cause difficulties in swallowing or breathing.</i> | |

| | | |
|--|--|---|
| Patent ductus arteriosus (PDA) | <p>Occurs when the ductus arteriosus (a connection between the left pulmonary artery and aorta) fails to close. The ductus arteriosus normally undergoes functional closure within a few hours after birth via smooth muscle contraction to ultimately form the ligamentum arteriosum.</p> |  |
| Postductal coarctation of the aorta | <p>Occurs when the aorta is abnormally constricted. A postductal coarctation (A) is found distal to the origin of the left subclavian artery and inferior to the ductus arteriosus.</p> <p>A preductal coarctation of the aorta (B) in which the constriction is located superior to the ductus arteriosus occurs less commonly.</p> |  |

▪ **Development of the venous system:**

The general pattern develops mainly from three pairs of veins: the **vitelline veins**, **umbilical veins**, and **cardinal veins** that empty blood into the sinus venosus. These veins undergo remodeling due to a left → right shunting of venous blood to the right atrium. Most anomalies of the venous system occur as a result of persistence of the veins on the left side of the body that normally regress during the left → right shunting of blood.

| Table 22-7: Correspondence of embryonic veins to their derivative adult counterparts: | |
|---|-------|
| Embryonic | Adult |

| | |
|------------------------|---|
| Vitelline veins | <ul style="list-style-type: none"> ○Portion of the IVC, hepatic veins and sinusoids, ductus venosus, portal vein, inferior mesenteric vein, superior mesenteric vein, splenic vein |
| Umbilical veins | <ul style="list-style-type: none"> ○Right → Degenerates early in fetal life ○Left → Ligamentum teres |
| Cardinal veins | <ul style="list-style-type: none"> ○Anterior → SVC, internal jugular veins ○Posterior → Portion of IVC, common iliac veins ○Subcardinal → Portion of IVC, renal veins, gonadal veins ○Supracardinal → Portion of IVC, intercostal veins, hemiazygos vein, azygos vein |

| Table 22-8: Clinical considerations in Formation of venous system: | |
|---|--|
| Disease | Cause |
| Double IVC | Occurs when the left supracardinal vein persists, forming an additional inferior vena cava below the level of the kidneys. |
| Left SVC | Occurs when the left anterior cardinal vein persists, forming a superior vena cava on the left side. The right anterior cardinal vein abnormally regresses. |
| Double SVC | Occurs when the left anterior cardinal vein persists, forming a superior vena cava on the left side. The right anterior cardinal vein also forms a superior vena cava on the right side. |
| Absence of the hepatic portion of the IVC | Occurs when the right vitelline vein fails to form a segment of the inferior vena cava. Consequently, blood from the lower part of the body reaches the right atrium via the azygos vein, hemiazygos vein, and superior vena cava. |

Fetal Circulation:

- Approximately 40% of the cardiac output perfuses the placenta and returns to the heart via the umbilical venous system (Umbilical vein $SO_2 = 80\%$, the most saturated fetal blood). Half this blood supplies the liver, and the rest passes via the ductus venosus to the IVC, where it meets the desaturated systemic venous drainage from the lower body. Selective streaming of these two flows minimizes mixing with the well-oxygenated blood from the ductus venosus, which is directed posterior and leftward in the IVC.
- The blood from the IVC enters the RA, and further streaming occurs via the anatomical configuration of the Eustachian valve and the upper margin of the foramen ovale to split the stream of blood into an anterior rightward stream that enters the right atrium and a posterior leftward stream (well-oxygenated ductus venosus blood) to the LA ($LA\ SO_2 = 70\%$). This blood is ejected by the LV to supply the heart and brain.
- Desaturated blood returning from the upper body via the SVC along with the desaturated blood from the coronary sinus (60% of the venous return) is directed through the tricuspid valve into the RV ($RV\ SO_2 = 55\%$).
- The pulmonary vascular resistance is very high (as the lungs are not expanded). So, only 8% of the combined ventricular output passes to the pulmonary circulation; the remainder passes directly via the ductus arteriosus to the descending aorta. The right atrial pressure is higher than the left, reflecting the greater blood flow through the right atrium.
- **At birth:** As the lungs are expanded, oxygen levels increase, and vasodilators including nitric oxide are released. The PVR falls to approximately half the systemic values by the first 24 hours of life. There is an eight- to ten-fold increase in pulmonary blood flow resulting in increased blood flow to the left atrium.

The placental circulation is interrupted, which increases SVR and decreases IVC return and RA filling.

The pressure difference between the RA and LA is reversed, and this closes the flap valve of the foramen ovale. The ductus arteriosus begins shunting left to right before it begins to constrict due to the production of bradykinin stimulated by increasing oxygenation and the fall in circulating prostaglandins.

Left to Right Shunt Lesions

Atrial Septal Defect (ASD)

ASD occurs as an isolated anomaly in 3-10% of all congenital heart defects. It is more common in females than in males. About 30-50% of children with CHDs have an ASD as part of the cardiac defect.

Pathophysiology:

○ In patients with ASD, the direction of the shunt is from left to right, and the magnitude of the left-to-right shunt is determined by the **size of the defect** and the **compliance of the RV and LV**. Because the compliance of the RV is greater than that of the LV, a left-to-right shunt is present. An L-R shunt occurs through the defect, with a volume overload to the RA and RV and an increase in pulmonary blood flow.

A significant shunt is defined as pulmonary-to-systemic blood flow ratio ($Q_p:Q_s$) $> 1.5:1$ or any shunt causing significant right heart dilatation.

○ **Four types of ASDs occur in the atrial septum:**

1. **Ostium secundum ASD** is in the central portion of the septum. It is the most common type (50-70% of ASD).
2. **Ostium primum ASD** (or partial endocardial cushion defect) is in the lower part of the septum (30% of ASD).
3. **Sinus venosus defect** is most commonly located at the entry of the SVC into the RA and rarely at the entry of the IVC into the RA (about 10% of all ASDs). Partial anomalous pulmonary venous return (PAPVR) is common with a sinus venous defect.
4. **Coronary sinus ASDs/unroofed coronary sinus** (extremely rare): The orifice of the coronary sinus becomes continuous with the left atrial chamber when a defect occurs in the wall separating the left atrium from the coronary sinus. The LA blood shunts through the defect and empties into the RA through the coronary sinus orifice, producing clinical pictures similar to other types of ASD.

Natural history:

- In ostium secundum ASD, spontaneous closure occurs in most patients with defects < 8 mm before 1.5 years of age. Spontaneous closure is not likely to occur if ASD > 8 mm or after 4 years of age.
- Spontaneous closure does not occur in ostium primum or sinus venosus type.
- If the defect is large and left untreated, pulmonary hypertension develops in adults in their 20s and 30s.
- With or without surgery, atrial arrhythmias (AF or flutter) may occur in adults (13% in patients > 40 years).

N.B:

- Mitral valve prolapse occurs in 20% of patients with either ostium secundum or sinus venosus defects.
- Sinus venosus defect at the IVC entry is commonly associated with anomalous drainage of the right lung into the IVC (“scimitar syndrome”).

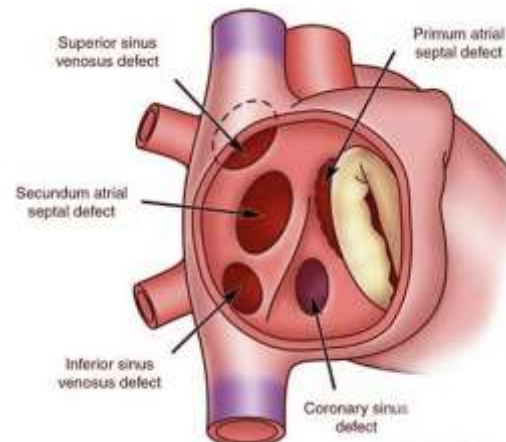


Figure 22-7: Types of Atrial septal defect.

Clinical Picture:

- **Manifestations:** The patients are usually asymptomatic. Cerebrovascular accident due to paradoxical embolization through an ASD is possible.
- **Auscultation:**
 - The heart murmur in ASD originates from increased blood flow through the tricuspid and pulmonary valves, producing mid-diastolic rumble at LLSB (relative TS) and ejection systolic murmur at the ULSB (relative PS).
 - A widely split and fixed S2 results from RBBB which results in delayed pulmonary valve closure.These typical auscultatory findings are usually absent in infants and toddlers, even in those with a large defect, because the RV is not compliant enough to result in a large L-R shunt in these patients.
- **ECG:** P-Pulmonale, RBBB (as the dilated RV prolongs the time required for RV depolarization).
- **Chest radiographs:** cardiomegaly (with RAE and RVE), increased pulmonary vascular markings (PVMs) and a prominent main pulmonary artery (MPA) segment when the shunt is significant.

Diagnostic work-up:

- **Echocardiography** is the first-line diagnostic technique, providing diagnosis and quantification.
 - ASD can best be seen in the subcostal four-chamber view. In secundum ASD, a dropout can be seen in the midatrial septum. The primum type shows a defect in the lower atrial septum; the SVC type of sinus venosus defect shows a defect in the posterosuperior atrial septum.
 - RV volume overload is the key finding and best characterizes the hemodynamic relevance of the defect (preferable to the shunt ratio).
 - TOE is required for precise evaluation of secundum defects before device closure, which should include sizing, exploration of the residual septum's morphology, the rim size and quality, exclusion of additional defects, and confirmation of a normal pulmonary venous connection.

- Other key information to be provided includes PAP and tricuspid regurgitation.
- **CMR** may be useful for assessment of RV volume overload, identification of inferior sinus venosus defect, quantification of pulmonary to systemic flow ratio (Qp:Qs), and evaluation of pulmonary venous connection (alternatively for the latter, use CCT).
- **Cardiac catheterization** is rarely necessary unless there are concerns about pulmonary hypertension (to measure PVR and its reversibility with vasodilators). The hallmark of an ASD is an increase in O₂ saturations of more than 5% from the SVC to the RA.
- **Exercise testing** should be performed in patients with PAH to exclude desaturation.

Management of ASD:

- In infants with CHF, medical management (with a diuretic) is recommended because of its high success rate and the possibility of spontaneous closure of the defect.
- **Indications of closure:** ASD closure is indicated in:
 - If CHF does not respond to medical management.
 - Presence of significant left-to-right shunt (significant RV enlargement) regardless of symptoms.
 - Patients with suspicion of paradoxical embolism in absence of PAH and LV disease.
- **Timing of closure:** In infants, closure is delayed until 2 to 4 years of age because the possibility of spontaneous closure exists.
- **Mode of closure:**
 - **Device closure:** is the method of choice for secundum ASD closure when there are adequate margins to accommodate the device. Closure rates are excellent with small residual shunts seen in < 5% of patients at 1 year of follow-up. Complications (extremely rare) include incomplete defect closure, device migration/erosion, and local vascular complications. After device closure, the patients are prescribed aspirin (3-5 mg/kg/day; max, 81 mg/day) for 6 months.
 - **Surgical closure:** indicated only when device closure is not considered appropriate (e.g ostium secundum not suitable for device closure, ostium primum, sinus venosus, or coronary sinus ASDs).
Atrial or nodal arrhythmias occur in 7-20% of postoperative patients.

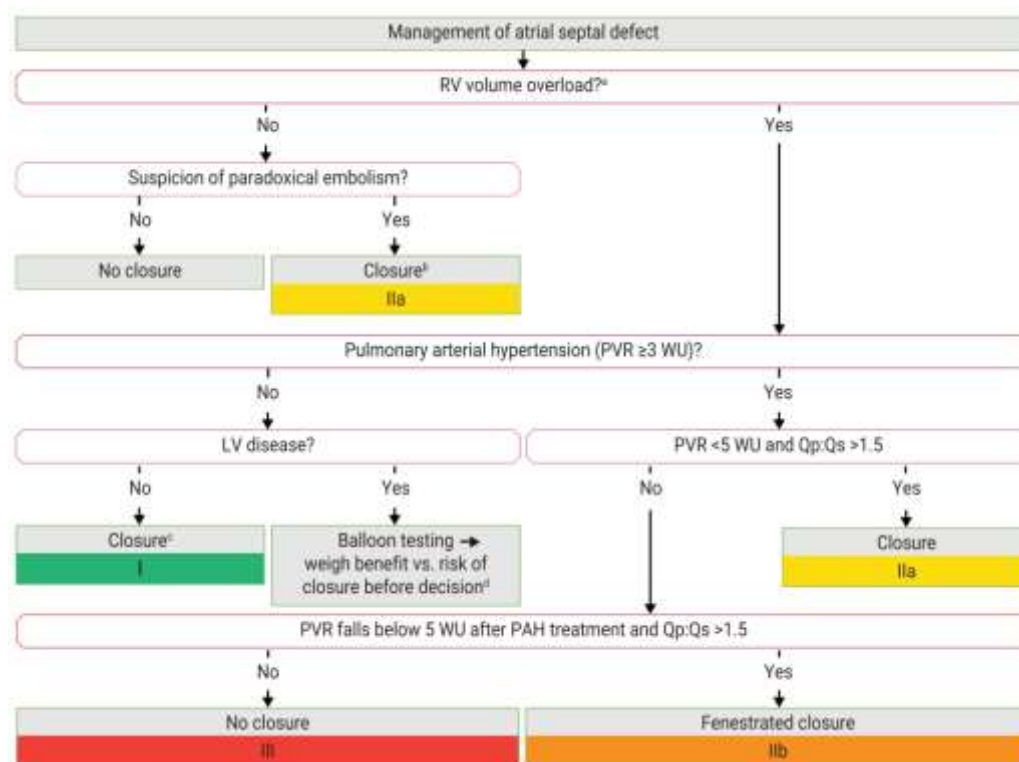


Figure 22-8: Management of atrial septal defect. A) RV enlargement with increased stroke volume. B) Providing there is no PAH or LV disease. C) In elderly patients not suitable for device closure, carefully weigh surgical risk vs. potential benefit of ASD closure. D) Carefully weigh the benefit of eliminating L-R shunt against the potential negative impact of ASD closure on outcome due to an increase in filling pressure (taking closure, fenestrated closure, and no closure into consideration).
Source: 2020 ESC Guidelines for the management of adult congenital heart disease.

Table 22-9: ESC Recommendations for intervention in atrial septal defect (native and residual):

| Recommendations | Class | Level |
|-----------------|-------|-------|
|-----------------|-------|-------|

| | | |
|--|------------|----------|
| <i>In patients with evidence of RV volume overload and no PAH (no non-invasive signs of PAP elevation or invasive confirmation of PVR < 3 WU in case of such signs) or LV disease, ASD closure is recommended regardless of symptoms.</i> | I | B |
| <i>Device closure is recommended as the method of choice for secundum ASD closure when technically suitable.</i> | I | C |
| <i>In elderly patients not suitable for device closure, it is recommended to carefully weigh the surgical risk against the potential benefit of ASD closure.</i> | I | C |
| <i>In patients with non-invasive signs of PAP elevation, invasive measurement of PVR is mandatory.</i> | I | C |
| <i>In patients with LV disease, it is recommended to perform balloon testing and carefully weigh the benefit of eliminating L-R shunt against the potential negative impact of ASD closure on outcome due to an increase in filling pressure (taking closure, fenestrated closure, and no closure into consideration).</i> | I | C |
| <i>In patients with suspicion of paradoxical embolism (exclusion of other causes), ASD closure should be considered regardless of size providing there is absence of PAH and LV disease.</i> | IIa | C |
| <i>In patients with PVR 3-5 WU, ASD closure should be considered when significant L-R shunt is present (Qp:Qs >1.5).</i> | IIa | C |
| <i>In patients with PVR ≥ 5 WU, fenestrated ASD closure may be considered when PVR falls below 5 WU after targeted PAH treatment and significant L-R shunt is present (Qp:Qs >1.5).</i> | IIb | C |
| <i>ASD closure is not recommended in patients with Eisenmenger physiology, patients with PAH and PVR ≥ 5 WU despite targeted PAH treatment, or desaturation on exercise ⁽¹⁾.</i> | III | C |

(1) There are limited data available for a precise cut-off, but by clinical experience, this would be given by a fall of SaO₂ < 90%.

Follow-up recommendations:

- Follow-up evaluation should include assessment of a residual shunt, RV size and function, TR and PAP by echocardiography, and assessment of arrhythmias by history, ECG, and if indicated Holter monitoring.
- Patients repaired at age < 25 years without relevant sequelae or residual (no residual shunt, normal PAP, normal RV, no arrhythmias) do not require regular follow-up.
- Patients with residual shunt, elevated PAP, or arrhythmias (before or after repair) and those repaired at adult age (particularly > 40 years) should be followed on a regular basis, including evaluation in specialized ACHD centres (intervals depending on the severity of residual problems).
- After device closure, regular follow-up during the first 2 years and then, every 3-5 years is reasonable.

Patent Foramen Ovale (PFO)

- PFO is a tunnel between the septum secundum and the superior margin of the septum primum. It represents the most common form of interatrial communication (in 25-30% of humans).
- **During fetal life**, the tunnel (foramen ovale) is open and allows a direct flow of IVC blood into the LA, sending blood with higher oxygen saturation to the LA (and eventually to the brain and coronaries).
- **Postnatally**, lung expansion promotes increase in pulmonary flow and therefore increase in pulmonary venous return and with it an increase in LA pressure. When the pressure in the LA exceeds that in the RA, the thin flap of the superior end of the septum primum is forced to shut against the septum secundum, thereby resulting in functional closure of the foramen. In most individuals, the foramen ovale is sealed shortly after birth, but for some reason, functional closure does not always occur, resulting in a small left-to-right atrial shunt.
- Recently, paradoxical embolization through PFO has been proposed as a potential cause of cryptogenic stroke in adults.

Ventricular Septal Defect

VSD is the most common form of CHD, accounting for 15-20% of all CHDs, not including those occurring as part of cyanotic CHDs.

Pathophysiology:

- The ventricular septum consists of a small membranous septum and a larger muscular septum. The muscular septum has three components: the inlet, trabecular (or muscular) and outlet (infundibular) septa.

- **Types of VSD:**

1.Membranous VSD (70%): The membranous septum is a relatively small area immediately beneath the aortic valve. A membranous VSD often involves a varying amount of muscular septum adjacent to it (i.e., perimembranous VSD). It may cause aortic valve regurgitation secondary to right or non-coronary cusp prolapse into the defect. The perimembranous VSD is frequently associated with PDA and COA.

The VSD seen with TOF is a large non-restrictive perimembranous defect with extension into the subpulmonary region.

2.Muscular VSD (20%): the defect varies in size from tiny defects to large ones. Most small defects close spontaneously. They frequently appear to be multiple when viewed from the right side.

3.Inlet VSD: inlet defect is located posterior and inferior to the perimembranous defect beneath the septal leaflet of the tricuspid valve. It is typically seen with endocardial cushion defects.

4.Outlet VSD (supracristal or infundibular or conal): outlet defect is located within the outlet (conal) septum, and part of its rim is formed by the aortic and pulmonary annulus.

- The direction of the shunt in acyanotic VSD is left to right. The magnitude of the shunt is determined by the **size** (not the location) of the defect and the **PVR**. With a small defect, a large resistance to the left-to-right shunt occurs at the defect, and the shunt does not depend on the level of PVR. With a large VSD, the left-to-right shunt depends largely on the level of PVR.
- In VSDs with small to moderate L-R shunts, volume overload is placed on the LA and LV (but not on the RV). With larger defects, the RV is also under volume and pressure overload, in addition to a greater volume overload on the LA and LV.

With a large VSD, pulmonary hypertension results. With a long-standing large VSD, pulmonary vascular obstructive disease (PVOD) develops, with severe pulmonary hypertension and cyanosis resulting from an R-L shunt. At this stage, surgical correction is nearly impossible.

- In subarterial infundibular or supracristal VSD, the aortic valve may prolapse through the VSD, with resulting AR and reduction of the VSD shunt. The prolapse may occasionally occur with the perimembranous VSD.
- The bundle of His is related to the posteroinferior quadrant of perimembranous defects and the superoanterior quadrant of inlet muscular defects. Defects in other parts of the septum are usually unrelated to the conduction tissue.

Natural history:

- Perimembranous and muscular VSDs: spontaneous closure can occur. It occurs more frequently with small defects, more often in the first year of life. Large defects tend to become smaller with age.
- Inlet and infundibular VSDs do not become smaller or close spontaneously.
- CHF develops in infants with a large VSD but usually not until 6 or 8 weeks of age, when the PVR drops below a critical level.
- PVOD may begin to develop as early as 6 to 12 months of age in patients with a large VSD.
- When a large VSD is left untreated, irreversible changes take place in the pulmonary arterioles, producing PVOD or Eisenmenger's syndrome. Because the PVR is notably elevated at this stage, the magnitude of the left-to-right shunt decreases. This results in removal of the volume overload placed on the LV as well as the LA. Therefore, the heart size returns to normal except for a prominent PA segment, and the ECG evidence of LVH disappears, leaving only RVH because of the persistence of pulmonary hypertension.

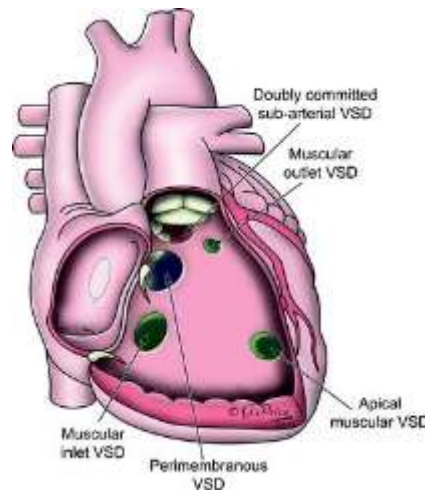


Figure 22-9: Types of VSD.

Clinical Picture:

○ Manifestations:

- Small VSD: patients are asymptomatic, with normal growth and development.
- Large VSDs: delayed growth and development, repeated chest infections, CHF, and decreased exercise tolerance are relatively common.
- If PVOD occurs: cyanosis and a decreased level of activity may result.

○ Auscultation:

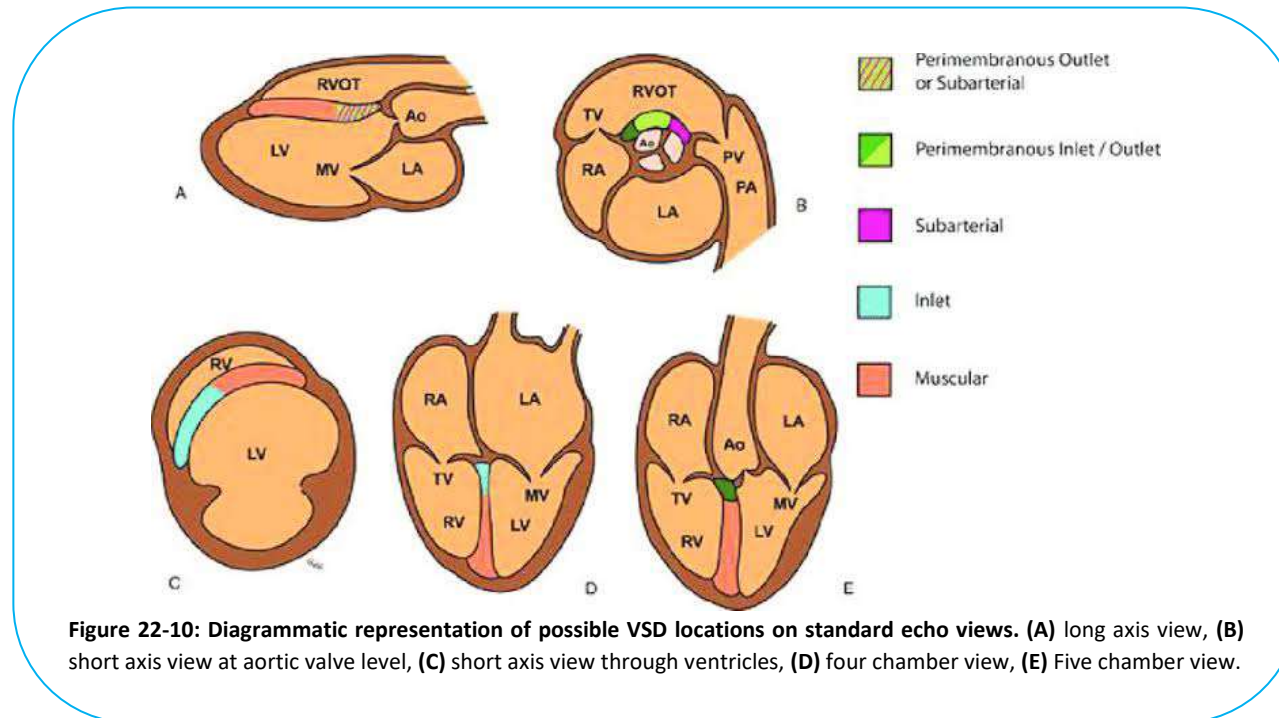
- Small VSD: regurgitant systolic murmur (holosystolic or less) maximally audible at the LLSB.
- Large VSD: apical diastolic rumble is audible, which represents a relative stenosis of the mitral valve due to large pulmonary venous return to the LA.
- With infundibular VSD, early diastolic murmur of AR may be audible (due to herniation of an aortic cusp).
- If pulmonary hypertension occurs: S2 may split narrowly, and the intensity of the P2 increases.

- **ECG findings:** Small VSD: normal. Moderate VSD: LVH ± LAH. Large VSD: biventricular hypertrophy ± LAH. PVOD: pure RVH.
- **Chest radiographs:** cardiomegaly of varying degrees with enlargement of the LA, LV, and possibly the RV. Pulmonary vascular markings are increased. In PVOD, the heart is no longer enlarged and the MPA and the hilar pulmonary arteries are notably enlarged, but the peripheral lung fields are oligemic.

Diagnostic work-up:

- **Echocardiography** is the key diagnostic technique, in general providing the diagnosis and assessment of disease severity. Key findings to provide are location, number, and size of defects, severity of LV volume overload, and estimated PAP.
The cardiac valves serve as markers of specific types of VSDs except for the muscular septum. The membranous VSD is closely related to the aortic valve, the inlet VSD to the tricuspid (or AV) valve, and the infundibular VSD to the semilunar valves.
- In the apical and subcostal “five-chamber” views, the membranous VSD is seen in the LVOT just under the aortic valve. In the parasternal short-axis view at the level of the aortic valve, it is seen adjacent to the tricuspid valve. These are the best views to confirm the membranous VSD.
- The inlet septum is best imaged in the apical or subcostal four-chamber view beneath the AV valves. It can also be seen in the parasternal short-axis view in the posterior interventricular septum at the levels between the mitral valve and the papillary muscle.
- The infundibular (or outlet) septum lies inferior to the semilunar valves. The subpulmonary, supracristal infundibular VSD lies under the pulmonary valve, and the subaortic infracristal VSD (TOF type) lies under the aortic valve.
- The entire ventricular septum seen at the papillary muscle level is the trabecular septum. For imaging of an apical muscular VSD, the transducer must be maximally angled toward the cardiac apex.
- AR due to prolapse of the right or non-coronary cusp must be checked for, especially in the case of outlet (supracristal) and high perimembranous VSDs. DCRV and sinus of Valsalva aneurysm must be excluded.
- **CMR** can serve as an alternative if echocardiography is insufficient, particularly for assessment of LV volume overload and shunt quantification.

- **Cardiac catheterization** is not required for the routine investigation of VSDs in infants. In children over one year of age with moderate or unrestrictive VSDs, it may be required to investigate the PVR.
- **Exercise testing** should be performed in patients with PAH to exclude desaturation.



Management of VSD:

- Small infants who have large VSDs and develop CHF with growth retardation are managed with diuretics and afterload reducing agents. If growth failure cannot be improved by medical therapy, the VSD should be operated on within the first 6 months of life. Surgery should be delayed for infants who respond to medical therapy.
- After 1 year of age, a significant left-to-right shunt with Qp/Qs ratio of at least 2:1 indicates that surgical closure is needed, regardless of PA pressure. Surgery is not indicated for small VSDs with Qp/Qs ratio less than 1.5:1.

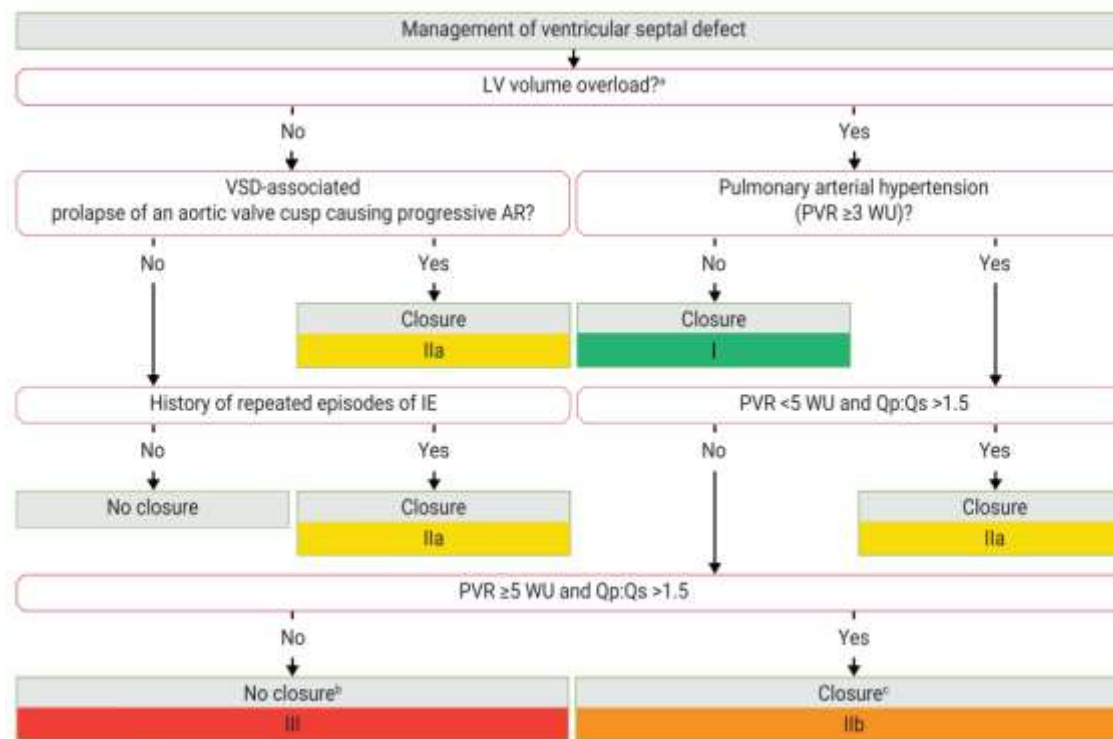


Figure 22-11: Management of ventricular septal defect. A) LV enlargement with increased stroke volume. B) Includes all patients with desaturation at rest (Eisenmenger physiology) or on exercise. C) Careful individual decision in expert centres is required. **Source:** 2020 ESC Guidelines for the management of adult congenital heart disease.

Table 22-10: ESC Recommendations for intervention in VSD (native and residual):

| Recommendations | Class | Level |
|-----------------|-------|-------|
|-----------------|-------|-------|

| | | |
|--|------------|----------|
| <i>In patients with evidence of LV volume overload and no PAH (no non-invasive signs of PAP elevation or invasive confirmation of PVR < 3 WU in case of such signs), VSD closure is recommended regardless of symptoms.</i> | I | C |
| <i>In patients with no significant L-R shunt, but a history of repeated episodes of IE, VSD closure should be considered.</i> | IIa | C |
| <i>In patients with VSD-associated prolapse of an aortic valve cusp causing progressive AR, surgery should be considered.</i> | IIa | C |
| <i>In patients who have developed PAH with PVR 3-5 WU, VSD closure should be considered when there is still significant L-R shunt (Qp:Qs >1.5).</i> | IIa | C |
| <i>In patients who have developed PAH with PVR ≥ 5 WU, VSD closure may be considered when there is still significant L-R shunt (Qp:Qs > 1.5), but careful individual decision in expert centres is required.</i> | IIb | C |
| <i>VSD closure is not recommended in patients with Eisenmenger physiology and patients with severe PAH (PVR ≥ 5 WU) presenting with desaturation on exercise. ⁽¹⁾</i> | III | C |

Follow-up recommendations:

○ Complications:

- Complete heart block occurs in up to 3% of patients undergoing surgical closure of VSD. Although the majority of heart block is transient, a small percentage of patients will develop permanent heart block and require pacemaker placement.
- Residual shunt occurs in < 5%. Intraoperative TEE echo has reduced the incidence of the hemodynamically significant residual shunt.

(1) There are limited data available for a precise cut-off, but by clinical experience, this would be given by a fall of SaO₂ < 90%.

- RBBB is almost always seen after perimembranous VSD closure. It is frequent in patients repaired via right ventriculotomy (in 50-90%). It occurs in up to 40% of the patients who had repair through RA.
- RBBB and left anterior hemiblock: occurs in < 10% of patients, is a controversial cause of sudden death.
- The incidence of neurologic complications is directly related to the circulatory arrest time.

○ **Follow up:**

- Development of AR or TR, degree of (residual) shunt, LV dysfunction, elevation of PAP, or development of double chambered RV (DCRV), should be excluded or assessed if present by echocardiography.
- Patients with more than small residual VSD, valvular lesions, or haemodynamic impairment (LV dysfunction or PAH) should be seen every year.
- In patients with a small VSD (native or residual, normal LV, normal PAP, asymptomatic) and no other lesion, 3-5-year intervals may be reasonable.
- After device closure, regular follow-up during the first 2 years and then, depending on the results, every 2-5 years is reasonable.
- After surgical closure without residual abnormality, 5-year intervals may be reasonable.

Atrioventricular Septal Defect (AVSD)

An AVSD (AV canal or endocardial cushion defect) is characterized by a defect in the centre of the heart (the atrio-ventricular junction) with a single valve structure straddling the centre of the heart. Thus, there is no true mitral or tricuspid valve; rather there is a left and right component of the common valve which is made up of mural leaflets and bridging leaflets (so called as they bridge the ventricular septum).

The anterior and posterior bridging leaflets are fused centrally, creating separate left- and right-sided orifices.

Complete AV canal occurs in about 5% of all CHDs. Most complete AVSDs occur in Down syndrome patients (> 75%), and most partial AVSDs occur in non-Down syndrome patients (> 90%). AVSD may occur in association with TOF and other forms of complex CHD.

Pathophysiology:

- **During fetal life**, the endocardial cushion tissue contributes to the closure of both the lower part of the atrial septum (i.e., ostium primum) and the upper part of the ventricular septum in addition to the formation of the mitral and tricuspid valves.
- The failure of normal development of this tissue may be either complete or partial:
 - **Complete AV canal** consists of ostium primum ASD, inlet VSD, and clefts in the anterior mitral leaflet and in the septal leaflet of the tricuspid valve, forming common anterior and posterior cusps of the AV valve.

When the ventricular septum is intact, the defect is termed **partial AV canal** or ostium primum ASD.

In complete AV canal, a single valve orifice connects the atrial and ventricular chambers, whereas in the partial form, there are separate mitral and tricuspid orifices.
- Both complete and partial forms of ECD are characterized by a deficiency of the inlet portion of the ventricular septum, with a “scooped-out” appearance of the muscular septum and an excessively long infundibular septum, as well as by an abnormal position of the aortic valve (i.e., displaced anterosuperiorly rather than being wedged between the right and left AV valves). The latter results in lengthening and narrowing of the LVOT, thereby producing the characteristic “goose-neck deformity” on angiocardiogram.
- In complete AVSD, hemodynamic changes depend on the extent of the VSD component and the degree of associated A-V valve incompetence. Large defects create a significant ventricular shunt with volume overload and CHF. The volume overload is exacerbated by any associated A-V valve regurgitation.

In contrast, hemodynamic changes in partial AVSD depend on the atrial shunt.
- The magnitude of the left-to-right shunt in complete AV canal is determined by the **level of PVR**.
- A direct communication between the LV and RA may occur as part of complete AV canal (or as an isolated defect unrelated to AVSD). The direction of the shunt is from the high-pressure LV to the low-pressure RA. The magnitude of the shunt is determined by the size of the defect, **regardless of the state of PVR**.

- In the majority of complete AV canal, the AV valve orifice is equally committed to the RV and LV. In some patients, however, the orifice is committed primarily to one ventricle, with hypoplasia of the other ventricle (i.e., “unbalanced” AV canal with RV or LV dominance). Hypoplasia of one ventricle may necessitate one ventricular repair (Fontan type operation).
- **Additional cardiac anomalies may include:** TOF (called “canal tet,” occurring in 6% of patients with AVSD), DORV with more than 50% overriding of the aorta (occurring in 6%), and TGA (occurring in 3%). Associated defects are rare in children with Down syndrome.

Natural history:

- CHF occurs 1 to 2 months after birth, and recurrent pneumonia is commonly seen. Without surgical intervention, many of these patients die by the age of 2 to 3 years. The survivors develop PVOD and die in late childhood or as young adults. Children with Down syndrome and AVSD begin to develop PVOD earlier in infancy.
- In partial AVSD, spontaneous closure of the defect does not occur. CHF (due to major MR) may develop in childhood earlier than with secundum ASD. Pulmonary hypertension (i.e., PVOD) develops in adulthood.

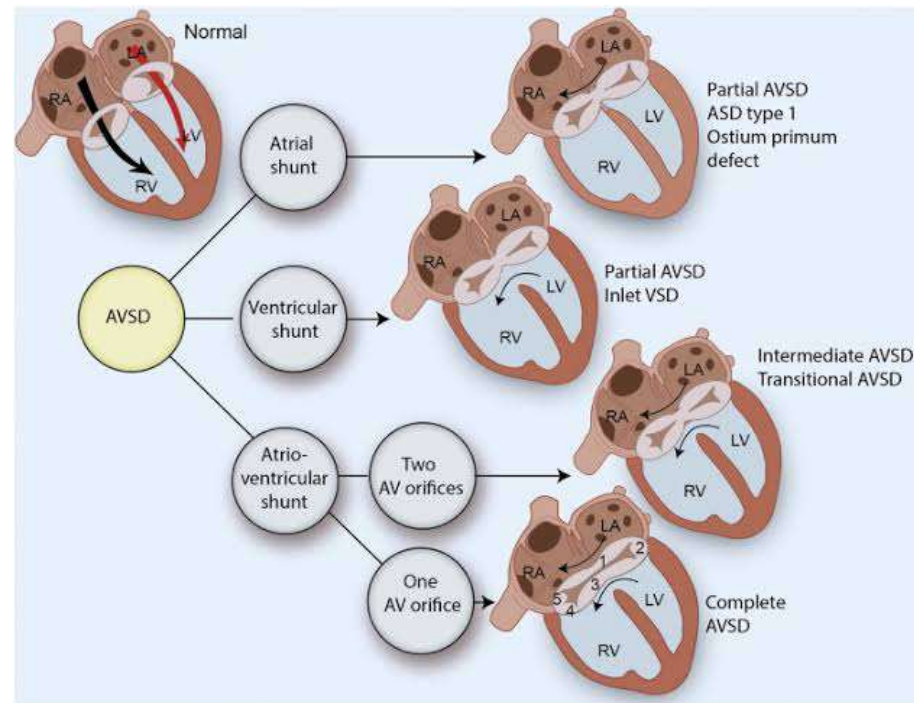


Figure 22-12: Illustration of AVSD types. Source: Calkoen EE, Hazekamp MG, Blom NA, et al. Atrioventricular septal defect: From embryonic development to long-term follow-up. International journal of cardiology. 2016 Jan 1;202:784-

Clinical Picture:

- **Symptoms:**
 - **Complete AV canal:** Failure to thrive, recurrent chest infections, and signs of CHF during early infancy.
 - **Partial AV canal:** patients with ostium primum ASD are usually asymptomatic during childhood.
- **Auscultation:**

- **Complete AV canal:** The S1 is accentuated. The S2 narrowly splits, and the P2 increases in intensity. Ejection systolic murmur at the LUSB, and a mid-diastolic rumble at the LLSB (relative tricuspid stenosis). Systolic murmur of mitral regurgitation is occasionally present.
- **Partial AV canal:** the same as secundum ASD.
- **ECG finding:** “Superior” QRS axis + RVH or RBBB + prolonged PR interval.
The abnormal QRS axis occurs as the AV node is positioned posterior and inferior to the coronary sinus (not due to axis deviation or any of the hemodynamic abnormalities). The bundle of His and the left bundle branch are displaced posteriorly. This accounts for an abnormal activation sequence of the ventricles (prolonged AV conduction, left-axis deviation).
- **Chest radiographs** always show cardiomegaly with increased pulmonary vascular markings.

Diagnostic work-up:

- **Echocardiography** is the key diagnostic technique. It provides assessment of each anatomic component of the AVSD (size of the ASD, VSD, and AV valve orifices, anatomy of leaflets, chordal attachment), the severity and exact substrate of AV valve regurgitation, the magnitude and direction of intracardiac shunting, LV and RV function, PAP, and assessment of the presence/absence of LVOTO.
- The apical and subcostal four-chamber views are most useful in evaluating the anatomy and the functional significance of the defect. These views show both ostium primum ASD and inlet muscular VSD.
- A combined use of the subcostal transducer position and the parasternal short-axis examination may show a cleft in the mitral valve, the presence of bridging leaflets, the number of AV valve orifices (e.g., double orifice mitral valve), and the AV valve leaflets.
- The subcostal “five-chamber” view may image a goose-neck deformity, which is characteristic of an angiocardiographic finding.
- **CMR** is indicated when additional quantification of ventricular volumes and function, AV valve regurgitation, or intracardiac shunting is required for decision making.

- **Cardiac catheterization** is required in case of non-invasive signs of PAP elevation (calculated systolic PAP > 40 mmHg or indirect signs when PAP cannot be estimated) to determine PVR.
- **Exercise testing** should be performed in patients with PAH to exclude desaturation.

Management of AVSD:

○ **Complete AV canal:**

- The presence of complete AVSD indicates the need for surgery (usually at age of 2-4 months) as most of these infants have CHF that is unresponsive to medical therapy. Because of the early development of POVD in patients with Down syndrome and complete AVSD, complete repair should be performed earlier.
- Patients with “unbalanced” AV canal with severe hypoplasia of the LV and low PA pressure may receive a combination of the Damus-Kaye-Stansel operation and Fontan operation (see “Single Ventricle”).

- **Partial AV canal:** The presence of a partial AV canal (or primum ASD) is an indication for surgical repair. Elective surgery can be performed in asymptomatic children between 2 and 4 years of age. Surgery can be performed earlier in infants with CHF, failure to thrive, MR, or a common atrium.

| Table 22-11: ESC Recommendations for intervention in atrioventricular septal defect: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Complete AVSD: | | |
| <i>Surgical repair is not recommended in patients with Eisenmenger physiology, and patients with PAH (PVR ≥5 WU) presenting with desaturation on exercise.⁽¹⁾</i> | III | C |
| <i>For recommendations on intervention see also recommendations for intervention in VSD</i> | | |
| Partial AVSD (primum ASD): | | |

(1) There are limited data available for a precise cut-off, but by clinical experience, this would be given by a fall of SaO₂ < 90%

| | | |
|---|------------|----------|
| <i>Surgical closure is recommended in patients with significant RV volume overload and should only be performed by a congenital cardiac surgeon.</i> | I | C |
| <i>For further details see recommendations for intervention in ASD</i> | | |
| AV valve regurgitation: | | |
| <i>Valve surgery, preferably AV valve repair, is recommended in symptomatic patients with moderate to severe AV valve regurgitation and should be performed by a congenital cardiac surgeon.</i> | I | C |
| <i>In asymptomatic patients with severe left-sided AV valve regurgitation, valve surgery is recommended when LVEDS ≥ 45 mm ⁽¹⁾ and/or LVEF $\leq 60\%$ provided other causes of LV dysfunction are excluded.</i> | I | C |
| <i>In asymptomatic patients with severe leftsided AV valve regurgitation, preserved LV function (LVEDS < 45 mm and/or LVEF $> 60\%$), high likelihood of successful valve repair, and low surgical risk, intervention should be considered when atrial fibrillation or systolic PAP > 50 mmHg is present.</i> | Ila | C |
| Left ventricular outflow tract obstruction: | | |
| <i>See recommendations for intervention in SubAS</i> | | |

Follow-up recommendations:

Complications:

- Development or progression of A-V valve regurgitation (commonest late problem), requiring repair.
- Sinus node dysfunction resulting in bradyarrhythmias may occur.

(1) Cut-off refers to average-sized adults and may require adaption in patients with unusually small or large stature.

- Although complete heart block occurs rarely (in < 5% of patients), it occurs more frequently when mitral valve replacement is required (up to 20% of patients).
- Postoperative arrhythmias (usually supraventricular).

Follow up:

- Lifelong regular follow-up of all patients with an AVSD, operated and unoperated, is recommended.
- The frequency of outpatient visits depends on the presence and severity of residual abnormalities. A patient with a surgically repaired AVSD without significant residual abnormalities should be seen at least every 2-3 years. In the case of residual abnormalities, the intervals should be shorter.

Patent Ductus Arteriosus (PDA)

PDA is the persistent communication between the proximal left PA and the descending aorta just distal to the left subclavian artery.

Pathophysiology:

- The media of the arterial duct consists of spirally arranged smooth muscle, and the intima is thicker than the aorta. After birth, the media contracts, thus shortening and occluding the duct. The subintimal layers proliferate and the duct thus closes permanently within 2-3 weeks of birth. Persistent patency of the duct in a full-term infant is defined as patency beyond three months of age.
- The magnitude of the left-to-right shunt is determined by the **size of the PDA** when the ductus is small and by the **level of PVR** when the ductus is large.
- With a long-standing large ductus, pulmonary hypertension and PVOD may develop with a resulting bidirectional shunt at the ductus level which may produce cyanosis only in the lower half of the body (i.e., differential cyanosis). The heart size returns to normal because of the reduced magnitude of the shunt.

Clinical Picture:

- **Manifestations:** The patients are asymptomatic when the ductus is small. When the defect is large, signs of CHF may develop. Bounding peripheral pulses with wide pulse pressure is characteristic of a large PDA. If pulmonary hypertension develops, a L-R shunt results in cyanosis only in the lower half of the body.
- **Auscultation:** Continuous (machinery) murmur best audible at the ULSB or left infraclavicular area. An apical diastolic rumble is audible with a large-shunt PDA (owing to relative mitral stenosis).
- **ECG findings** (similar to VSD): normal or LVH in small to moderate PDA; BVH in large PDA; RVH if PVOD develops.
- **Chest radiographs** (similar to VSD): normal with a small-shunt PDA. With a large-shunt PDA, cardiomegaly (with LA and LV enlargement) and increased pulmonary vascular markings are present. With PVOD, the heart size is normal, with a marked prominence of the MPA and hilar vessels.

Natural history:

- Spontaneous closure of a PDA is rare in full-term infants and children. This is because the PDA in term infants results from a structural abnormality of the ductal smooth muscle rather than a decreased responsiveness of the ductal smooth muscle to oxygen.
- CHF or recurrent pneumonia develops if the shunt is large.
- Pulmonary vascular obstructive disease may develop if a large PDA with pulmonary hypertension is left untreated.
- Although rare, an aneurysm of PDA may develop and possibly rupture in adult life.

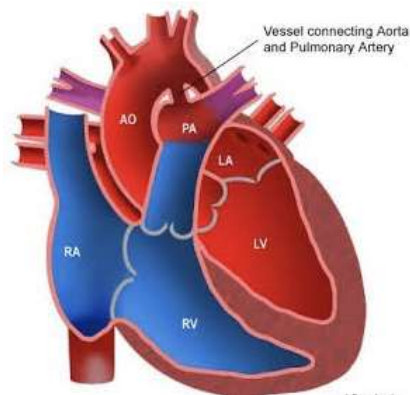


Figure 22-13: Patent ductus arteriosus illustration.

Differential Diagnosis

The following conditions require differentiation from PDA because they may present with a heart murmur similar to that of PDA and/or with bounding pulses.

- **Coronary AV fistula:** the murmur is audible over the precordium, not at the ULSB.
- **Systemic AV fistula:** a wide pulse pressure with bounding pulse, CHF, and a continuous murmur over the fistula [head or liver] are characteristic.
- **Pulmonary AV fistula:** a continuous murmur over the back, cyanosis, and clubbing in the absence of cardiomegaly.
- **Venous hum:** an innocent condition that disappears when the patient is supine.
- Murmurs of **collaterals in patients with COA or TOF:** audible in the intercostal spaces.
- **VSD + AR:** maximally audible at the MLSB or LLSB. it is actually a to-and-fro murmur, rather than a continuous murmur.
- **Absence of pulmonary valve:** a to-and-fro murmur, or “sawing-wood sound” at the ULSB, large central pulmonary arteries on chest radiographs, RVH on ECG, and cyanosis.
- **Aortopulmonary septal defect (AP window):** bounding peripheral pulses, a murmur resembling that of VSD, and signs of CHF.
- **Peripheral PA stenosis:** a continuous murmur may be audible all over the thorax, unilateral or bilateral.

- **Ruptured sinus of Valsalva aneurysm:** sudden onset of chest pain and severe heart failure, a continuous murmur or a to-and-fro murmur, and often Marfan features.

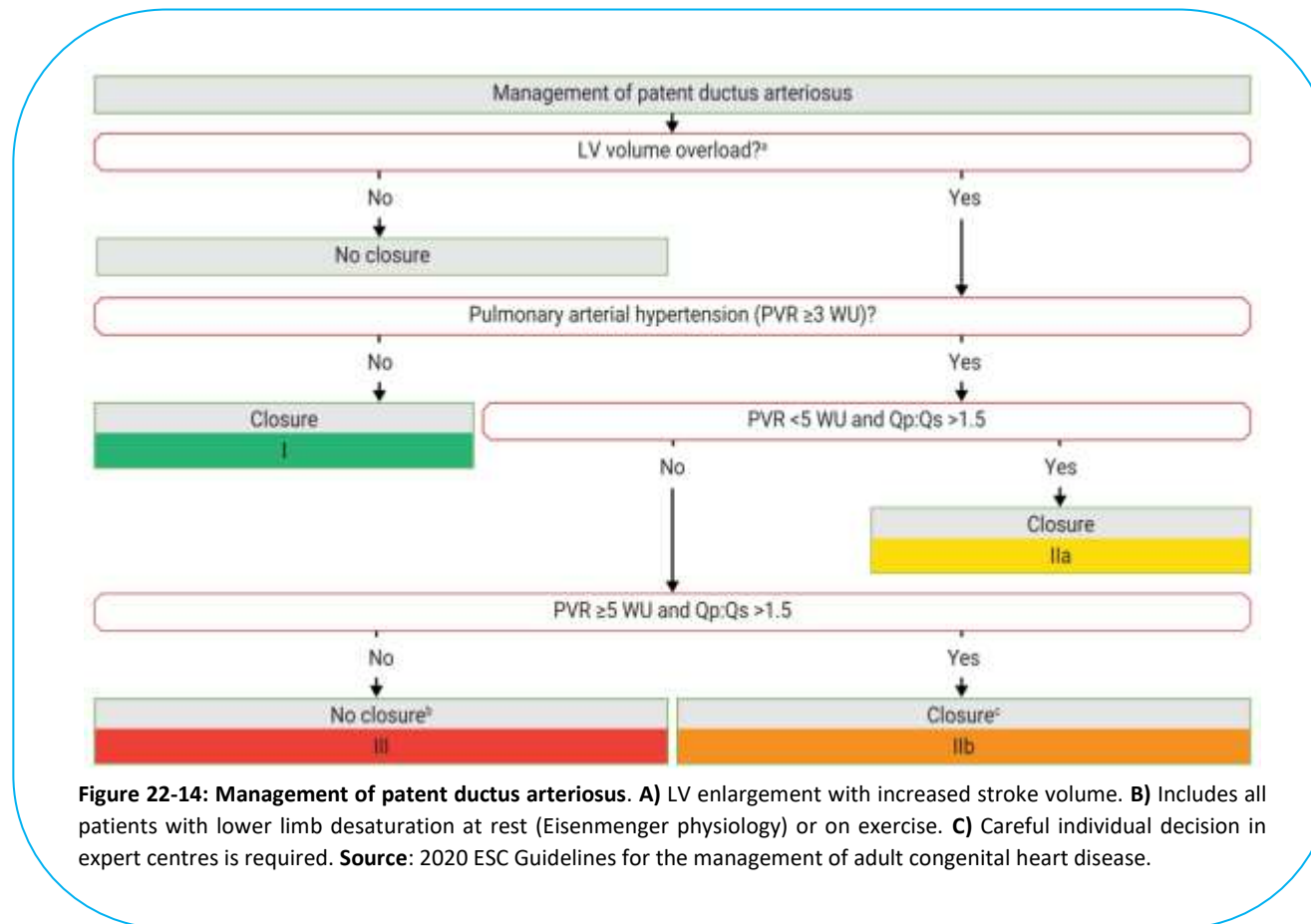
Diagnostic work-up:

- **Echocardiography** provides the diagnosis, degree of LV volume overload, PAP, PA size, and right heart changes.
 - The PDA can be imaged in most patients. Its size can be assessed in high parasternal or suprasternal view.
 - Doppler studies that are performed with the sample volume in the PA immediately proximal to the ductal opening provide important functional information.
 - The dimensions of the LA and LV provide an indirect assessment of the magnitude of the left-to-right ductal shunt. The larger the shunt, the greater the dilatation of these chambers.
- **CMR** is indicated when additional quantification of LV volumes and quantification of Qp:Qs is needed.
- **CCT** can further evaluate the anatomy where required.
- **Cardiac catheterization** is required in the case of non-invasive signs of PAP elevation (calculated systolic PAP > 40 mmHg or indirect signs when PAP cannot be estimated) to determine PVR. Measurement of pulmonary blood flow is challenging in this setting. Measurement of oxygen saturation in both left and right PAs is mandatory.
- **Exercise testing** should be performed in patients with PAH to exclude desaturation of lower limbs.

Management of PDA:

- Closure of PDA is definitely indicated in patients with hemodynamically significant PDA with CHF, failure to thrive, pulmonary overcirculation, or enlargement of the LA and LV.
- In patients with Eisenmenger syndrome or pulmonary vascular obstructive disease, the response of PVR to balloon occlusion or pulmonary vasodilator (e.g., nitric oxide) is tested in cardiac catheterization laboratory. If a good response is obtained, closure is advised. If the response is poor or equivocal, closure may not be recommended.
- Transcatheter occlusion of PDA has become a standard of care (Success rate > 95%).

- Surgical closure is reserved for patients in whom a nonsurgical closure technique is not considered applicable. Complications are rare and usually related to the severe prematurity. Complications include: left recurrent laryngeal nerve injury (hoarseness), the left phrenic nerve (paralysis of the left hemidiaphragm), or the thoracic duct (chylothorax).



| Table 22-12: ESC Recommendations for intervention in PDA: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>In patients with evidence of LV volume overload and no PAH (no non-invasive signs of PAP elevation or invasive confirmation of $PVR < 3$ WU in case of such signs), PDA closure is recommended regardless of symptoms.</i> | I | C |
| <i>Device closure is recommended as the method of choice when technically suitable.</i> | I | C |
| <i>In patients who have developed PAH with $PVR 3-5$ WU, PDA closure should be considered when there is still significant L-R shunt ($Qp:Qs > 1.5$).</i> | IIa | C |
| <i>In patients who have developed PAH with $PVR \geq 5$ WU, PDA closure may be considered when there is still significant L-R shunt ($Qp:Qs > 1.5$) but careful individual decision in expert centres is required.</i> | IIb | C |
| <i>PDA closure is not recommended in patients with Eisenmenger physiology and patients with lower limb desaturation on exercise ⁽¹⁾.</i> | III | C |

Follow-up recommendations:

- Echocardiographic evaluation to assess LV size and function, PAP, residual shunt, and associated lesions.
- Patients with no residual shunt, normal LV, and normal PAP do not require regular follow-up after 6 months.
- Patients with LV dysfunction and patients with residual PAH should be followed at intervals of 1-3 years, depending on severity, including evaluation in specialized ACHD centres.

(1) There are limited data available for a precise cut-off, but by clinical experience, this would be given by a fall of $SaO_2 < 90\%$.

Partial Anomalous Pulmonary Venous Connection

Pathophysiology:

- This is a rare congenital cardiac defect in which some of the pulmonary veins (most commonly from the right lung) are connected to the right atrium or systemic veins rather than to the left atrium.
- The right PVs may drain into the SVC, often associated with sinus venous ASD, or drain into the IVC in association with an intact atrial septum and bronchopulmonary sequestration. The left PVs drain either into the left innominate vein or into the coronary sinus.
- PAPVD causes a left-to-right shunt (similar to that seen with ASD). The magnitude of the pulmonary blood flow is determined by the number of anomalous PVs, the presence and size of the ASD and the PVR.

Natural history:

If PAPVR is undetected, cyanosis and exertional dyspnea may develop during the third and fourth decades, resulting from pulmonary hypertension and PVOD. Pulmonary infections are common in patients with anomalous drainage of the right pulmonary veins to the IVC.

N.B: Scimitar Syndrome: This consists of PAPVD of the right pulmonary veins draining into the IVC (the 'scimitar' sign created by this large venous channel curving around the RA to reach the IVC). This is associated with pulmonary arterial anomalies to the supply to the right lung (typically the right lower lobe supplied by a collateral vessel from the abdominal aorta), but arterial supply can be normal.



Figure 22-15: Chest x-ray showing a scimitar-like abnormal shadow in the right lower lung field (arrows). Source: Ashida K, Itoh A, Naruko T, et al. Familial scimitar syndrome: three-dimensional visualization of anomalous pulmonary vein in young sisters. Circulation. 2001 Jun 26;103(25):e126-7..

Clinical Picture:

- **Manifestations:** Children with PAPVR are usually asymptomatic. Adults may become symptomatic from chronic right-sided volume overload.
- **Auscultation:** when associated with ASD, the S2 is split widely and fixed. When the atrial septum is intact, the S2 is normal. A mid-diastolic rumble (due to relative tricuspid stenosis) may be present.
- **ECG:** Normal or may show RVH or RBBB.
- **Chest radiographs:** RAE, RVE, and increased pulmonary vascular markings.
- **Echocardiography:** isolated PAPVC can be missed even with careful echocardiography.

The inability to visualize all four pulmonary veins in the presence of mild dilatation of the RA and RV strongly suggests the diagnosis of PAPVR, especially in the presence of a demonstrable ASD.
- **Cardiac MRI** can make correct diagnosis of the condition without catheterization.

Management:

Indications for surgery follow the principals of recommendation for ASD closure, but technical suitability for repair and operative risk must be weighed against the potential benefit of intervention.

It is unusual for a single anomalous pulmonary venous connection of only one pulmonary lobe to result in a sufficient volume load to justify surgical repair.

Obstructive Lesions

RVOT Obstruction

Pathophysiology:

- **RVOTO may be valvular, subvalvular (infundibular), supravalvular, or within RV cavity (subinfundibular):**
 - 1. Valvular PS:** the pulmonary valve is thickened, with fused or absent commissures and a small orifice. The RV is usually normal in size in children with PS. In neonates with critical PS (with a nearly atretic valve), right-sided structures (including the RV, TV, RVOT and pulmonary artery) are commonly underdeveloped.
Dysplastic valves (consisting of thickened, irregular, immobile tissue and a variably small pulmonary valve annulus) are frequently seen with Noonan's syndrome.
 - 2. Subvalvular (Infundibular) stenosis** usually occurs in combination with other lesions, particularly VSD, TOF, and secondary to valvular pulmonary stenosis (reactive myocardial hypertrophy). At the infundibular level, and to some extent the sub-infundibular level, the obstruction tends to be dynamic, meaning that the orifice narrows during systole.
 - 3. Sub-infundibular stenosis**, or double-chambered RV (DCRV). It is caused by aberrant hypertrophied muscular bands (running between the ventricular septum and the anterior wall) divide the RV cavity into a proximal high-pressure chamber and a distal low-pressure chamber (double-chambered RV). It is commonly associated with a VSD.
 - 4. Supravalvular PS** (Pulmonary arterial stenosis): the stenosis may be located in the main branches or more peripherally; it may be discrete or diffuse (hypoplastic) or there may be frank occlusion, and it may occur as single or multiple stenoses. Stenosis may be secondary to previous placement of a PA band or at a previous shunt site. A diameter narrowing $\geq 50\%$ is usually considered to be significant and would be expected to have a pressure gradient and result in hypertension in the proximal PA. Commonly associated defects are pulmonary valve stenosis, VSD, and TOF. It seldom occurs in isolation, and may occur in Williams Beuren syndrome, Noonan syndrome, congenital rubella syndrome, or Alagille syndrome.
- In general, three pathophysiologic changes occur in obstructive lesions such as PS (or AS). They are: **(1)** systolic ejection murmur on auscultation, **(2)** hypertrophy of the responsible ventricle, and **(3)** poststenotic dilatation.

- Depending on the severity of PS, a varying degree of RVH develops. The RV is usually normal in size, but in newborns with critical PS, the RV is hypoplastic.

Natural history:

The severity of the obstruction is usually not progressive in mild PS, but it tends to progress with age in moderate or severe PS. CHF may develop in patients with severe stenosis.

Sudden death is possible in patients with severe stenosis during heavy physical activities.

Clinical Picture:

○ **Manifestations:**

- Mild PS: Usually asymptomatic.
- Severe stenosis: exertional chest pain or syncope (even sudden death with strenuous exercise).
- Neonates with critical PS (who have hypoplastic RV and R-L atrial shunt) are cyanotic and tachypneic.

○ **Auscultation:** The S2 may split widely, and P2 may be diminished. A systolic ejection murmur is best audible at the ULSB and transmits fairly well to the back and axillae. The louder and longer the murmur, the more severe is the stenosis. Neonates with critical PS may have only a faint heart murmur, if any.

○ **ECG:** Mild PS: normal. Moderate PS: RAD and RVH. Severe PS: RAH and RVH with “strain” pattern. Neonates with critical PS may show LVH (due to hypoplastic RV and relatively large LV).

○ **Chest radiographs:** normal heart size and a prominent MPA segment. PVMs are normal but may be decreased in severe PS.

Diagnostic work-up:

○ **Echocardiography:** size, shape, and function of the RV can be assessed and the exact position/level of the RVOTO can be visualized, as well as pulmonary valve, main PA, and proximal PA branches.

Doppler ultrasound is used for measurements of flow velocities across an obstruction to assess severity. The severity of PS (by peak pressure gradient) may be classified as follows:

(1) Mild: < 40 mmHg (or RV pressure < 50% of LV pressure).

(2) Moderate: gradient 40-64 mmHg (or RV pressure 50-75% of LV pressure).

(3) Severe: > 64 mmHg (or RV pressure \geq 75% of LV pressure).

N.B:

If the narrowing is elongated, or if more than one stenosis is present in series (e.g. subvalvular and valvular), application of the Bernoulli equation will lead to an overestimation of the pressure gradient. Doppler flow velocity of TR then gives a more reliable estimation of RV pressures and with that, severity of the RVOTO.

- **CMR and CCT** are the methods of choice to visualize pulmonary dilation and peripheral PS. They frequently provide additional important information identifying the level(s) of obstruction, and assessment of RV volumes, pulmonary annulus, outflow tract and artery dimensions, and differential pulmonary blood flow.
- **Cardiac catheterization** may be required to confirm the extent, severity, and level of obstruction (e.g. DCRV).

Management of RVOT obstruction:

Newborns with critical PS: These cyanotic neonates (with severe pulmonary valve stenosis, hypoplastic RV, and a R-L atrial shunt) require emergency treatment to reduce mortality.

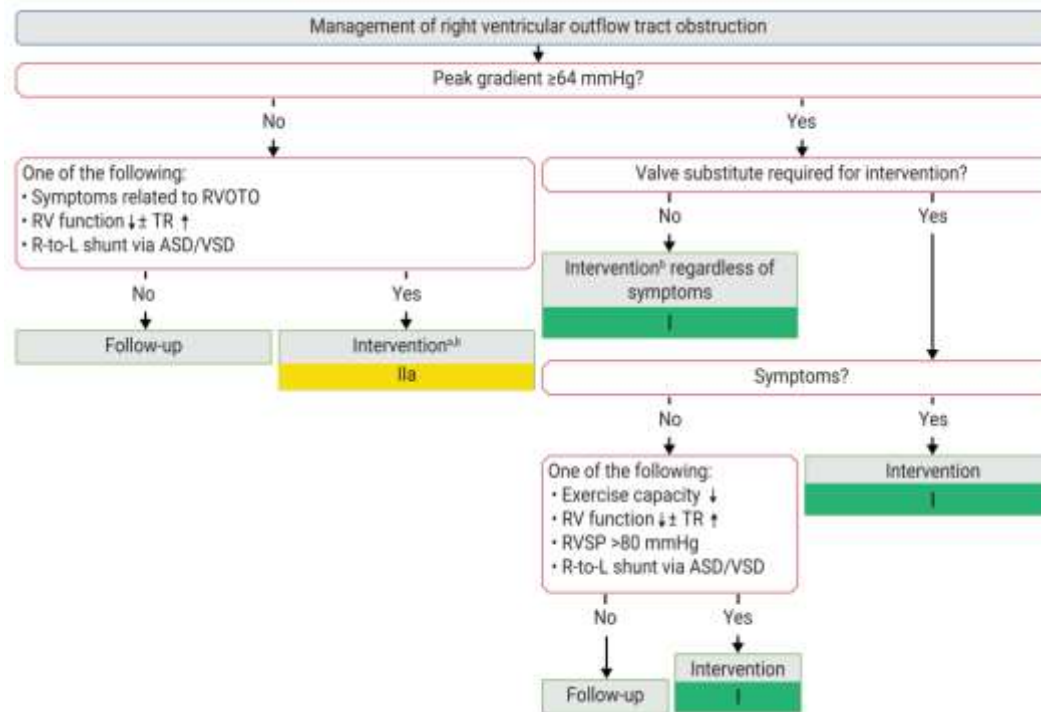


Figure 22-16: Management of right ventricular outflow tract obstruction. A) In peripheral PS, regardless of symptoms, catheter interventional treatment should be considered if > 50% diameter narrowing and RVSP > 50 mmHg and/or related reduced lung perfusion is present. B) In valvular PS, balloon valvuloplasty is the intervention of choice if anatomically suitable. **Source:** 2020 ESC Guidelines for the management of adult congenital heart disease.

Table 22-13: ESC Recommendations for intervention in right ventricular outflow tract obstruction:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In valvular PS, balloon valvuloplasty is the intervention of choice, if anatomically suitable.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Provided that no valve replacement is required, RVOTO intervention at any level is recommended regardless of symptoms when the stenosis is severe (Doppler peak gradient is > 64 mmHg ⁽¹⁾).</i> | I | C |
| <i>If surgical valve replacement is the only option, it is indicated in patients with severe stenosis who are symptomatic ⁽²⁾.</i> | I | C |
| <i>If surgical valve replacement is the only option in patients with severe stenosis who are asymptomatic, it is indicated in the presence of one or more of the following:</i> <ul style="list-style-type: none"> ○ <i>Objective decrease in exercise capacity.</i> ○ <i>Decreasing RV function and/or progression of TR to at least moderate.</i> ○ <i>RVSP > 80 mmHg.</i> ○ <i>R-L shunting via an ASD or VSD</i> | I | C |
| <i>Intervention in patients with a Doppler peak gradient < 64 mmHg should be considered in the presence of one or more of the following:</i> <ul style="list-style-type: none"> ○ <i>Symptoms related to PS.</i> ○ <i>Decreasing RV function and/or progressive TR to at least moderate.</i> ○ <i>R-L shunting via an ASD or VSD.</i> | IIa | C |
| <i>Peripheral PS, regardless of symptoms, should be considered for catheter interventional treatment if > 50% diameter narrowing, and RVSP > 50 mmHg, and/or related reduced lung perfusion is present.</i> | IIa | C |

(1) RVSP estimated from TR velocity should confirm severe PS.

(2) The threshold for intervention is higher when a valve substitute is required because long-term risks, such as endocarditis and re-intervention for prosthetic valve failure, need to be taken into account.

Follow-up recommendations:

- Complications of the balloon procedure are more common than in older patients, with a mortality rate of up to 3%, and major complication rate of 3.5%.
- About 15% of the patients require reintervention (either repeat valvuloplasty or surgery for infundibular stenosis or dysplastic valve) at a later time.
- After surgical or catheter intervention, a residual PR may need reintervention later in life for patients who become symptomatic or when progressive RV dilatation or dysfunction occurs.
- Patients with RVOTO need lifelong follow-up with regular echocardiographic imaging. The frequency of follow-up depends on the severity of the lesion, but most patients will need a yearly visit. Patients with mild valvular or mild residual PS need to be seen only once in 5 years.

LVOT Obstruction

Pathophysiology:

- **LVOT Obstruction can occur at the valvular, subvalvular or supra-ventricular levels:**
 - **Valvular Aortic Stenosis:** The most common cause for congenital valvular aortic stenosis is BAV (with a fused commissure), and less commonly by a unicuspid valve (with one lateral attachment) or stenosis of the tricuspid (tricommissural) valve. Many cases of bicuspid aortic valve are non-obstructive during childhood.
 - **Supra-ventricular Aortic Stenosis:** is an annular constriction at the *sinotubular junction*. It may occur as a characteristic feature of *Williams syndrome* or be isolated/ familial, which are respectively caused by deletion of the elastin gene located on chromosome 7q11.23 or a mutation in this same gene. Williams accounts for about 60-70% of all cases of supra-aortic stenosis.

- **Subvalvular (subaortic) stenosis** may be either discrete (simple membrane or fibromuscular ridge) **or** diffuse tunnel-like fibromuscular narrowing (tunnel stenosis).
 - **Discrete subaortic stenosis/membrane** is more common than the tunnel stenosis and is often associated with other lesions such as VSD, PDA, or COA. Occasionally, its development follows surgical interventions, such as closure of VSD or PA banding.
 - **Tunnel-like subaortic stenosis** is often associated with hypoplasia of the aortic valve ring and the ascending aorta. It may be a part of Shone complex (comprising supramitral ring, parachute mitral valve, subaortic stenosis, and COA).
- LVH may develop if the stenosis is severe. A poststenotic dilatation of the ascending aorta is present in valvular AS. AR usually develops with subaortic stenosis.

Natural history:

- Chest pain, syncope, and even sudden death (1–2% of cases) may occur in children with severe AS. Heart failure occurs with severe AS during the newborn period or later in adult life.
- Progressive aortic dilatation occurs in patients with BAV. Up to 80% of patients with a BAV will develop ascending aortic dilatation. Despite the progressive nature of the condition, the incidence of aortic dissection is rare in children and adolescents with BAV.
- Mild stenosis frequently becomes more severe with time. The stenosis may worsen with aging as the result of calcification of the valve cusps (requiring valve replacement surgery in some adult patients).
- Progressive AR is possible in discrete subaortic stenosis. The jet of the subaortic stenosis damages the aortic valve with resulting AR.

Clinical Picture:

- **Manifestations:** Mild to moderate AS: are asymptomatic. Severe AS: Exertional chest pain or syncope. CHF develops within the first few months of life with critical AS.

Blood pressure is normal in most patients, but a narrow pulse pressure is present in severe AS.

Patients with supralvalvular AS may have a higher systolic pressure in the right arm than in the left (due to the jet of stenosis directed into the innominate artery, the so-called Coanda effect).

- **Auscultation:** An ejection click may be audible with valvular AS. A harsh systolic ejection murmur is best audible at the second right and left intercostal spaces, with good transmission to the neck and frequently to the apex. In symptomatic infants with critical AS, the heart murmur may be absent or faint.
- **ECG:** normal in mild cases. LVH with or without a strain pattern is seen in more severe cases.
- **Chest radiographs:** usually normal in children, but a dilated ascending aorta may be seen occasionally in valvular AS. A significant cardiomegaly develops with CHF or substantial AR.

Diagnostic work-up:

- **Echocardiography** is diagnostic. 2D echo shows the anatomy of the aortic valve (bicuspid, tricuspid, or unicuspid) and that of subvalvular and supralvalvular AS. The Doppler pressure gradient is best obtained in the apical “five-chamber” view. The Doppler pressure gradient (instantaneous gradient) is approximately 20% higher than the peak-to-peak systolic pressure gradient obtained during cardiac catheterization.

The severity of AS by Doppler peak (and mean) gradients and by peak-to-peak catheter gradient may be classified as follows.

- **Mild:** Mean Doppler < 25 mm Hg [or peak-to-peak gradient <30 mmHg].
- **Moderate:** Mean Doppler 25-40 mmHg [or peak-to-peak gradient 30-50 mmHg].
- **Severe:** Mean Doppler > 40 mm Hg [or peak-to-peak gradient > 50 mmHg]

For the discrete membranous stenosis, one should note **(1)** the length of the membrane, **(2)** the pressure gradient across the obstruction, **(3)** the distance of the membrane from the aortic valve, **(4)** the extension of the membrane onto the aortic or mitral valve, **(5)** the presence of aortic regurgitation, and **(6)** associated cardiac lesions.

- **TOE** may provide anatomical details about valve dysfunction or AVA planimetry in non-calcified valves.

- **CMR/CCT**, is useful for detailed evaluation of supra-ventricular anatomy, in particular, when multilevel LVOTO is present or for (pre-operative) assessment of coronary artery anatomy and other aortic or aortic branch lesions (e.g. carotid and renal artery stenosis), and central and branch PAs.

CCT has become particularly important for the quantification of valve calcification when assessing AS severity in low gradient AS, although it should be noted that aortic valve stenosis in young patients is not necessarily associated with significant calcification.

- **Cardiac catheterization** is only required if non-invasive evaluation yields uncertain results, for evaluation of coronary arteries, or when percutaneous balloon angioplasty is considered.

Management of severe LVOT obstruction:

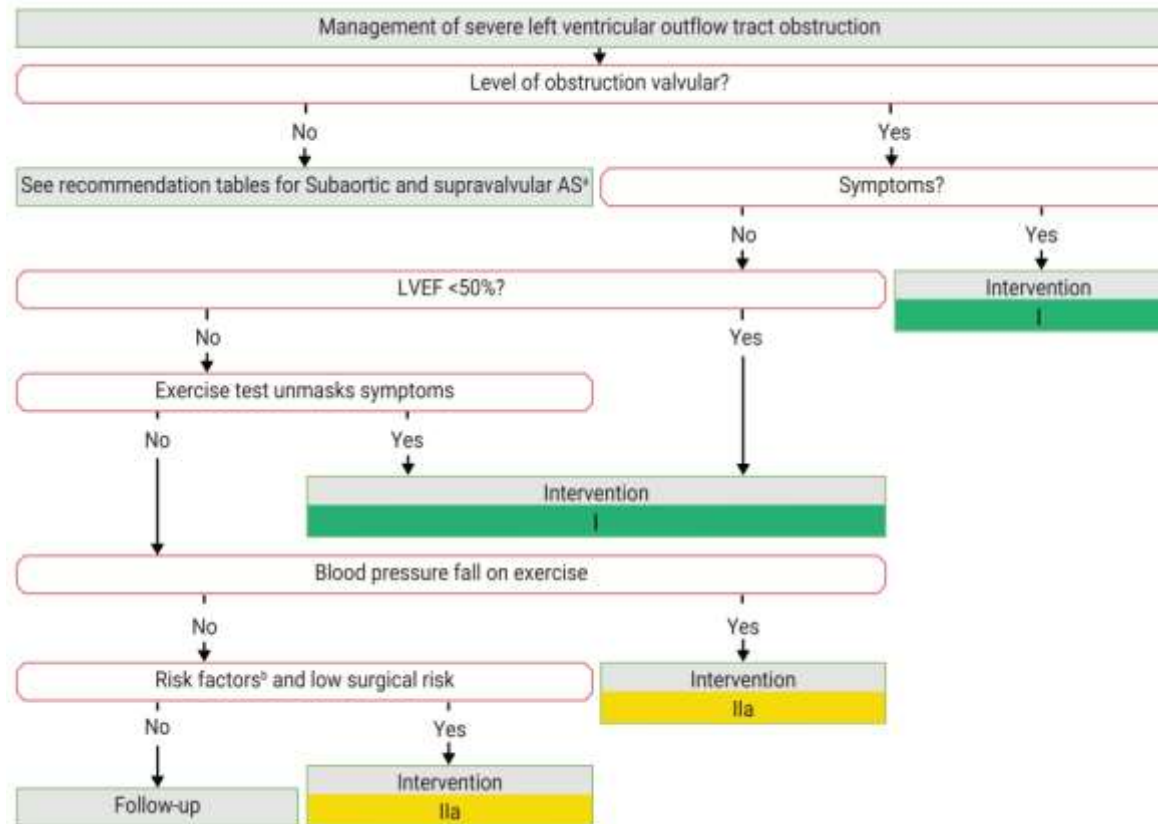


Figure 22-17: Management of severe left ventricular outflow tract obstruction. A) There are fundamental differences in management decisions compared to valvular AS, particularly because a valve substitute with its consequences is generally not required. **B)** Peak velocity > 5.5m/s; severe calcification + peak velocity progression ≥ 0.3 m/s/y; markedly elevated neurohormones (> 3-fold age- and sex-corrected normal range); severe PH (systolic PAP > 60 mmHg without other explanation). **Source:** 2020 ESC Guidelines for the management of adult congenital heart disease.

| Table 22-14: ESC Recommendations for intervention in LVOT obstruction: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Symptomatic patients with aortic valve stenosis: | | |
| <i>In symptomatic patients with severe high-gradient AS (mean gradient ≥ 40 mmHg), intervention is recommended.</i> | I | B |
| <i>Intervention is indicated in symptomatic patients with severe low-flow, low-gradient (mean gradient < 40 mmHg) AS with reduced EF and evidence of flow (contractile) reserve excluding pseudosevere AS.</i> | I | C |
| Asymptomatic patients with severe aortic valve stenosis: | | |
| <i>Intervention is indicated in asymptomatic patients with severe AS and an abnormal exercise test showing symptoms on exercise clearly related to AS.</i> | I | C |
| <i>Intervention is indicated in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF $< 50\%$) not due to another cause.</i> | I | C |
| <i>Intervention should be considered in asymptomatic patients with severe AS when they present with a fall in blood pressure below baseline during exercise testing.</i> | IIa | C |
| <i>Intervention should be considered in asymptomatic patients with normal EF and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present:</i> <ul style="list-style-type: none"> ○ Very severe AS defined by a $V_{max} > 5.5$ m/s. ○ Severe valve calcification and a rate of V_{max} progression ≥ 0.3 m/s/year. ○ Markedly elevated BNP levels (> 3-fold age and sex-corrected normal range) confirmed by repeated measurements without other explanation. ○ Severe PH (systolic PAP at rest > 60 mmHg confirmed by invasive measurement) without other explanation. | IIa | C |

| | | |
|---|------------|----------|
| Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery: | | |
| <i>Surgery is recommended when patients with severe AS undergo surgery of the ascending aorta or of another valve, or CABG.</i> | I | C |
| <i>Patients with moderate AS undergoing CABG surgery or surgery of the ascending aorta or another valve should be considered for additional valve replacement.</i> | IIa | C |
| Supravalvular aortic stenosis: | | |
| <i>In patients with symptoms (spontaneous or on exercise test) and mean Doppler gradient ≥ 40 mmHg, surgery is recommended.</i> | I | C |
| <i>In patients with mean Doppler gradient < 40 mmHg, surgery is recommended when one or more of the following findings are present:</i> <ul style="list-style-type: none"> ○Symptoms attributable to obstruction (exertional dyspnoea, angina, syncope). ○LV systolic dysfunction (EF $< 50\%$ without other explanation). ○Surgery required for significant CAD or valvular disease. | I | C |
| <i>Patients with mean Doppler gradient ≥ 40 mmHg ⁽¹⁾ but without symptoms, LV systolic dysfunction, LVH, or abnormal exercise test may be considered for repair when the surgical risk is low.</i> | IIb | C |
| Subaortic stenosis: | | |
| <i>In symptomatic patients (spontaneous or on exercise test) with a mean Doppler gradient ≥ 40 mmHg ⁽¹⁾ or severe AR, surgery is recommended.</i> | I | C |
| <i>Asymptomatic patients should be considered for surgery when one or more of the following findings are present:</i> <ul style="list-style-type: none"> ○Mean gradient < 40 mmHg but LVEF $< 50\%$. | IIa | C |

(1) Doppler-derived gradients may overestimate the obstruction and may need confirmation by left heart catheterization.

| | | |
|---|------------|----------|
| <ul style="list-style-type: none"> ○ AR is severe and LVESD > 50 mm (or 25 mm/m² BSA) and/or EF < 50%. ○ Mean Doppler gradient is ≥ 40 mmHg and marked LVH present. ○ Mean Doppler gradient is ≥ 40 mmHg and there is a fall in blood pressure below baseline on exercise. | | |
| <p>Asymptomatic patients may be considered for surgery when one or more of the following findings are present:</p> <ul style="list-style-type: none"> ○ Mean Doppler gradient is ≥ 40 mmHg, LV is normal (EF > 50% and no LVH), exercise testing is normal, and surgical risk is low. ○ Progression of AR is documented, and AR becomes more than mild (to prevent further progression). | IIb | C |

Follow-up recommendations:

- Lifelong and regular follow-up is required, and the intervals depend upon the degree of stenosis severity.
- Annual follow-up is required for all patients who had a balloon or surgical procedure done for the aortic valve because risk of development of significant AR and discrete subaortic membrane recurrence.
- Recurrence of discrete subaortic stenosis occurs in 25-30%. Risk factors for recurrence include: **(A)** younger age (< 4 years), **(B)** high pressure gradient (> 50 mmHg), **(C)** proximity of the membrane to the aortic valve (< 6 mm), and **(D)** extension of the membrane to the aortic or mitral valves.
- CMR or CCT of the aorta is recommended in patients with a native BAV, patients with a history of isolated valve replacement where the ascending aorta is not well visualized on TTE, and in patients with root/ascending diameters > 40 mm.

Coarctation of the Aorta (CoA)

CoA occurs in 4-8% of all cases of CHD. It is more common in males (male-to-female ratio= 2:1).

Pathophysiology:

- CoA is considered as part of a generalized arteriopathy, and not only as narrowing of the aorta. It occurs as a discrete stenosis **or** as a long, hypoplastic aortic (arch) segment.
Typically, CoA is located in the area where the ductus arteriosus inserts, and rarely occurs ectopically (ascending, descending, or abdominal aorta).
- **In symptomatic infants with CoA:** During fetal life, the descending aorta is supplied mostly via right-to-left ductal flow because the amount of antegrade flow through the relatively small aortic arch and isthmus is reduced (due to associated cardiac defects such as aortic hypoplasia, abnormal aortic valve, VSD, and mitral valve anomalies). With ductal closure, a reduced antegrade aortic flow to the descending aorta produces symptoms early in life. Good collateral circulation has not developed in these infants.
- **In asymptomatic children with CoA:** During fetal life, the descending aorta is supplied by both normal amount of antegrade aortic flow through the aortic isthmus and normal ductal flow (because associated cardiac defects are rare in these children except for BAV). Good collateral circulation gradually develops between the proximal aorta and the distal aorta during fetal life. Major collateral circulation between the aortic segments proximal and distal to the coarctation comprises: **(A)** the internal mammary artery anteriorly, **(B)** arteries arising from the subclavian artery by way of the intercostal arteries, and **(C)** the anterior spinal artery.
- **Associated lesions** include: BAV (in up to 85% of all patients with CoA), SubAS, or SupraAS, (supra)mitral valve stenosis (including parachute mitral valve), Shone complex, ascending aortic aneurysm, or complex congenital heart defects.
- CoA can be associated with Turner and Williams syndromes. 30% of patients with Turner's syndrome, have CoA.
- **Extracardiac vascular anomalies** including: anomalous origin of the right subclavian artery (in 45% of cases), collateral arterial circulation, and intracerebral aneurysms (in up to 10% of patients with COA).

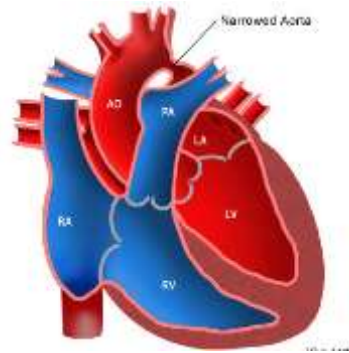


Figure 22-18: Coarctation of Aorta.

Clinical Picture:

• **Symptomatic Infants:**

- **Manifestations:** CHF (poor feeding, dyspnea) and renal failure (oliguria, anuria) with general circulatory shock may develop in the first 2 to 6 weeks of life.
- **Auscultation:** A loud S3 gallop and weak and thready pulses, without heart murmur, are common.
- **ECG:** A normal or rightward QRS axis and RVH or RBBB, rather than LVH.
- **Chest radiographs:** marked cardiomegaly and signs of pulmonary edema or pulmonary venous congestion.
- Early death from CHF and renal failure is possible.

• **Asymptomatic Children:**

- **Manifestations:** usually asymptomatic except for rare complaints of leg pain after exercise.
The pulse in the leg is absent or weak and delayed. Hypertension in the arm or the leg systolic pressure is equal to or lower than the arm systolic pressure (Hypertension develops due to the mechanical obstruction and the activation of RAAS pathways).

- **Auscultation:** An ejection click resulting from the BAV is frequently audible at the apex and/or base. Ejection systolic murmur is audible at the RUSB and LMSB and in the left interscapular area in the back. Continuous murmurs may be heard (due to collateral vessels).
- **ECG:** Leftward QRS axis and LVH, but it may be normal (in 20% of patients).
- **Chest radiographs:** normal or slightly enlarged heart. A “hourglass or 3 sign” on overpenetrated films. Rib notching may be seen in children after 5 years of age (due to the collaterals). “E sign” on the barium-filled esophagus may be present.
- The bicuspid aortic valve may cause stenosis and/or regurgitation later in life. If a COA is left untreated, LV failure, intracranial hemorrhage, or hypertensive encephalopathy may develop later in life.

Diagnostic work-up:

- **Office blood pressure measurement** in the upper and lower extremities is required. A blood pressure gradient between upper and lower extremities (systolic ≥ 20 mmHg) indicates significant CoA.
Ambulatory blood pressure measurements (right arm) are recommended to detect/confirm arterial hypertension (24-h mean systolic > 130 mmHg and/or diastolic > 80 mmHg).
- **Echocardiography** provides information regarding site, structure, and extent of CoA, LV function and LVH, associated cardiac abnormalities, and aortic and supra-aortic vessel diameters.
A diastolic tail in the descending aorta and diastolic forward flow in the abdominal aorta are findings of significant (re-)CoA.

Doppler gradients are not useful for quantification, neither in native nor in post-operative coarctation:

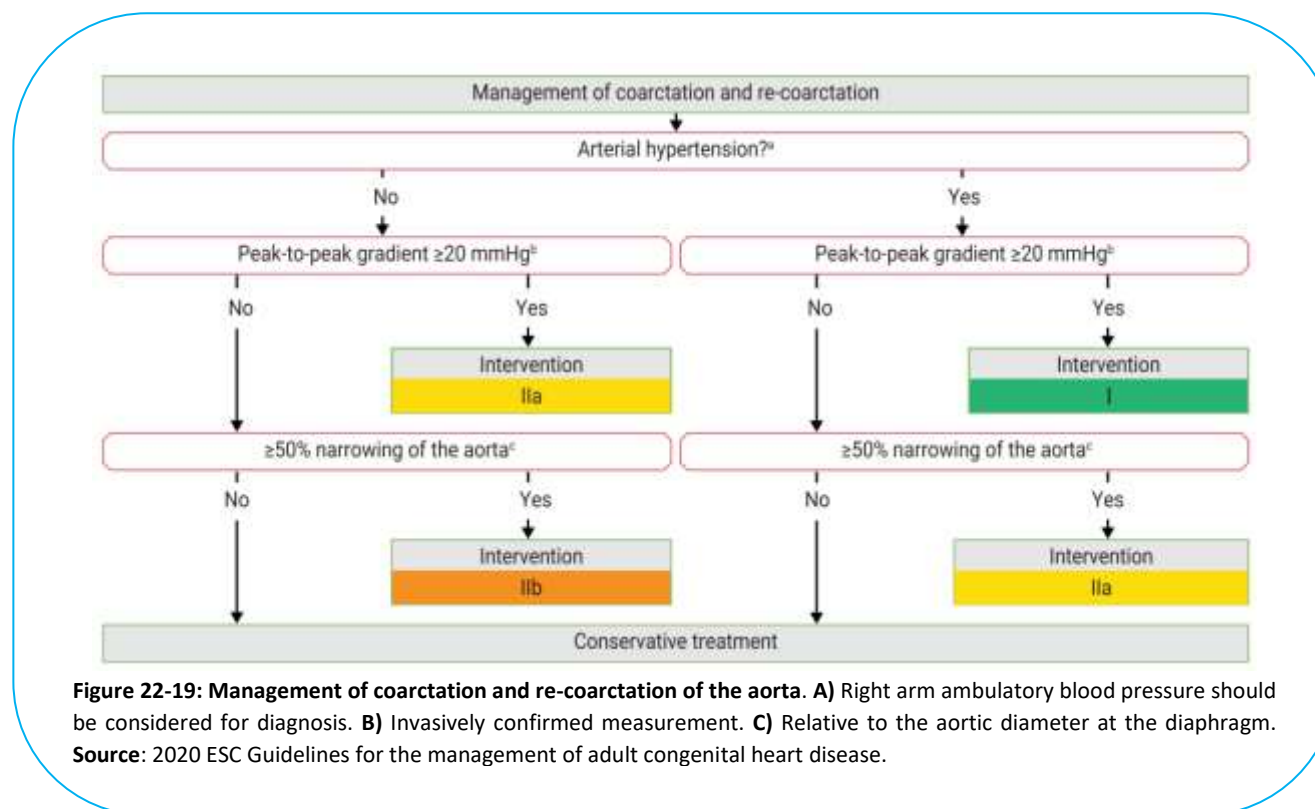
- In the presence of extensive collateral arteries, gradients are often underestimated.
- After surgical repair or stenting, increased systolic flow rates may develop, even in the absence of significant narrowing, due to decreased/absent aortic compliance and Doppler-related pressure recovery. The gradient is then overestimated.
- **CMR and CCT**, including 3D reconstruction, are the preferred non-invasive techniques to evaluate the entire aorta in adolescents and adults. Both depict site, extent, and degree of the aortic narrowing, the aortic arch and head and neck vessels, the pre and

post-stenotic aorta, and collaterals. Both methods detect complications such as aneurysms, false aneurysms, restenosis, or residual stenosis.

- **Imaging of intracerebral vessels** is indicated in the case of symptoms and/or clinical manifestations of aneurysms/rupture.
- **Cardiac catheterization with manometry** (peak-to-peak gradient ≥ 20 mmHg) indicates hemodynamically significant CoA in the absence of well-developed collaterals and is performed in the setting of interventional treatment. It should be noted that, in patients under general anesthesia, invasive measurement of gradient may be underestimated.

Management of coarctation and re-coarctation of the aorta:

Indications of intervention:



| Table 22-15: ESC Recommendations for intervention in coarctation and re-coarctation of the aorta: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>Repair of coarctation or re-coarctation (surgically or catheter based) is indicated in hypertensive patients with an increased non-invasive gradient between upper and lower limbs confirmed with invasive measurement (peak-to-peak ≥ 20 mmHg) with preference for catheter treatment (stenting), when technically feasible.</i> | I | C |
| <i>Catheter treatment (stenting) should be considered in hypertensive patients ⁽¹⁾ with $\geq 50\%$ narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is < 20 mmHg, when technically feasible.</i> | IIa | C |
| <i>Catheter treatment (stenting) should be considered in normotensive patients ⁽¹⁾ with an increased non-invasive gradient confirmed with invasive measurement (peak-to-peak ≥ 20 mmHg), when technically feasible</i> | IIa | C |
| <i>Catheter treatment (stenting) may be considered in normotensive patients with $\geq 50\%$ narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is < 20 mmHg, when technically feasible.</i> | IIb | C |

As coarctation is not a localized disease of the aorta, associated lesions that may require structural interventions have to be considered:

- Associated significant aortic valve stenosis or regurgitation (BAV).
- Aneurysm of the ascending aorta with a diameter > 50 mm or rapid progression of diameter.
- Aneurysm and false aneurysms at the previous CoA site.
- Symptomatic or large aneurysms of the circle of Willis.

(1) Right arm ambulatory blood pressure monitoring should be considered for the diagnosis of hypertension.

Management Strategy: Management is dictated by the age at presentation, complexity of the coarctation, and native versus recurrent coarctation.

○ **For neonates, infants and small children with native coarctation:**

- Surgery (preferably extended resection and end-to-end anastomosis) is recommended, especially when the COA is associated with complex anatomy.
- Balloon angioplasty is not a good choice because of its long-term risk of aneurysm.
- Stent placement is also not a good choice because it requires redilation at a later time, and the arteries are too small to accommodate a stent that can be dilated to adult size.
- It is reasonable to choose balloon angioplasty as a palliative strategy in neonates too sick for major surgical procedure.

○ **For small children with recurrent coarctation:**

- Balloon angioplasty without stent is a reasonable approach because the child is too small to receive a stent that can be dilated to adult size.
- For children with complex anatomy (e.g., tortuous segment of recoarctation), surgery should also be considered.

○ **For older children, adolescents and adults:**

- With a simple, native or recurrent coarctation, stent placement is a reasonable approach. (Only stents expandable to an adult size should be used.)
- Balloon angioplasty (without stent) is not a good choice because it is variably successful, and surgical reintervention may be required.

Follow-up recommendations:

- All CoA patients require regular follow-up at least every year since recoarctation is possible, with attention to: **(1)** BP differences in the arm and leg (recoarctation), **(2)** status of associated abnormalities such as bicuspid aortic valve or mitral valve disease, and **(3)** possible development of subaortic stenosis.

- Imaging of the aorta (preferably with CMR) is required to document post-repair or post-interventional anatomy and complications (restenosis, aneurysm, false aneurysm formation).
- Recommended imaging intervals are commonly every 3-5 years but also depend on baseline pathology.

Complications, Sequelae:

- **Recurring or residual CoA** may induce or aggravate systemic arterial hypertension and its complications.
- **Aneurysms of the ascending aorta** or at the intervention site present a risk of rupture and death. Patch repairs (e.g., with Dacron) are at particular risk of repair-site aneurysms, while interposition grafts are at particular risk of false aneurysms, and both should be imaged on a regular basis.
- **Hypertension:** The risk of hypertension is much less if the patient is repaired at < 5 years of age, but in older patients, up to 50% may still have hypertension requiring medical therapy.
- Attention is required for BAV, mitral valve disease, premature CAD, and berry aneurysms of the circle of Willis (routine screening in asymptomatic patients is not recommended).
- **Complications of surgery:**
 - Spinal cord ischemia producing paraplegia may develop after cross-clamping of the aorta during surgery, which is probably related to limited collateral circulation. This develops in 0.4% of cases.
 - Rebound hypertension may occur in the immediate post-operative period as a result of an increased sympathetic activity (with elevated norepinephrine level).
 - Recurrent laryngeal nerve injury, chylothorax, bleeding, and infection.

Interrupted Aortic Arch

This is defined as an interruption of luminal continuity between the ascending and descending aorta.

Pathophysiology:

- This extreme form of CoA is divided into three types according to the location of the interruption:
 - **In type A**, the interruption is distal to the left subclavian artery (occurring in 30% of patients).
 - **In type B**, the interruption is between the left carotid and left subclavian arteries (occurs in 43% of cases). DiGeorge syndrome occurs in about 50% of patients with type B interruption.
 - **In type C**, the interruption is between the innominate and left carotid arteries (occurs in 17% of cases).
- **Associated anomalies:** interrupted arch is usually associated with left-to-right intracardiac shunt: VSD (80%), persistent truncus arteriosus (10%) and aorto-pulmonary window (5-10%). A bicuspid aortic valve (60%), mitral valve deformity (10%), or subaortic stenosis (20%) may be present. DiGeorge syndrome occurs in at least 15% of these patients.

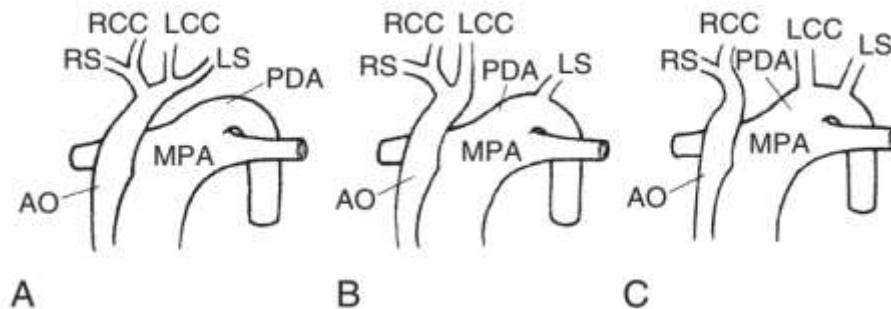


Figure 22-20: Three types of aortic arch interruption. AO, aorta; LCC, left common carotid; LS, left subclavian; MPA, main pulmonary artery; PDA, patent ductus arteriosus; RCC, right common carotid; RS, right subclavian. **Source:** Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Clinical Picture:

- **Manifestations:** Neonates present with respiratory distress, cyanosis, poor peripheral pulse, or circulatory shock seen in the first few days of life (when the arterial duct closes). Cardiac findings are nonspecific.

- **Chest radiographs:** cardiomegaly, increased PVM, and pulmonary edema. The upper mediastinum may be narrow (due to the absence of thymus, i.e., DiGeorge syndrome).
- **ECG** may show RVH.

Diagnostic Workup:

- **TTE** is diagnostic, showing interruption of the aorta arch, descending aorta continuing from the duct.
- **Cardiac CT or MRI** is more frequently used to clarify the anatomy before surgery.

Management

- **Medical:**

- PGE1 infusion, intubation, and oxygen administration.
- Workup for DiGeorge syndrome (i.e., serum calcium, FISH for 22q11.2 deletion) should be carried out.
- Citrated blood (that causes hypocalcemia by chelation) should not be transfused. Blood should be irradiated before transfusion in patients with DiGeorge syndrome.

- **Surgical:**

- Surgical repair of the interruption (primary anastomosis, Dacron vascular graft, or venous homograft) and closure of a simple VSD are recommended if possible.
- If associated with complex defects, repair of the interruption and PA banding are performed, with complete repair at a later time.

Cyanotic Congenital Heart diseases

Tetralogy of Fallot (TOF)

- TOF occurs in 5% to 10% of all CHDs. This is the most common cyanotic heart defect.
- TOF populations can be subdivided into:
 - Nonsyndromic patients (which represent the vast majority).
 - Syndromic patients (20%; e.g. microdeletion 22q11, trisomy 21, Alagille, Noonan, Williams, and Klippel Feil)
- The standardized mortality rate among patients with repaired TOF is almost twice as high as among patients with simple defects (ASD and VSD).

Pathophysiology:

- The original description of TOF included four abnormalities: **(1)** Non-restrictive VSD; **(2)** Overriding aorta (but < 50%); **(3)** RVOT obstruction (infundibular, valvular, supra-valvular) and/or branch PA stenosis; and **(4)** Consequent RV hypertrophy (RVH). Actually, only two abnormalities are required: a VSD large enough to equalize pressures in both ventricles and RVOT obstruction.
 - **VSD** is a perimembranous defect with extension into the infundibular septum.
 - **RVOTO** may be in the form of infundibular stenosis (50%), pulmonary valve stenosis (10%), or both (30%). The pulmonary annulus and the PA are usually hypoplastic. The pulmonary valve is atretic in 10% of the patients.
- Because of the non-restrictive VSD, systolic pressures in the RV and the LV are identical. Depending on the degree of the RVOT obstruction, an L-R, bidirectional, or R-L shunt is present. With a mild PS, an L-R shunt is present (“acyanotic/pink” TOF). With a more severe degree of PS, a predominant R-L shunt occurs (cyanotic TOF).
- In TOF with pulmonary atresia, the PBF is most commonly mediated through a PDA (70%) and less commonly through multiple aortopulmonary collateral arteries (MAPCAs, 30%). Collateral arteries arise most commonly from the descending aorta (occurring in two thirds of patients), less commonly from the subclavian arteries, and rarely from the abdominal aorta or its branches.

- In TOF with absent pulmonary valve, the annulus of the valve is stenotic and displaced distally. A massive aneurysmal dilatation of the PAs is present. The massive PA aneurysm develops during fetal life resulting from severe pulmonary regurgitation and an associated increase in RV stroke volume. The aneurysmal PAs compress anteriorly the lower end of the developing trachea and bronchi throughout fetal life, producing hypoplasia of the compressed airways.
- **Associated Anomalies:**
 - Right aortic arch is present in 25% of the cases, with some of them having symptoms of vascular ring.
 - Abnormal coronary arteries are present in about 5% of TOF (The most common abnormality is LAD arising from RCA and passing over the RVOT, which prohibits a surgical incision in the region).
 - Complete AV canal defect occurs in approximately 2% of patients with TOF, more commonly among patients with Down syndrome, called “canal tet.”
 - ToF is also associated with, bilateral SVCs (10%) and, as part of the family of cono-truncal anomalies, has an association with DiGeorge syndrome (15%).

Natural history:

- In TOF, Hypoxic spells may develop in infants.
- Polycythemia is common, but relative iron deficiency may be present (Normal hemoglobin or hematocrit values or decreased RBC indices indicate an iron-deficiency state in cyanotic patients). Brain abscess, cerebrovascular accident, and SBE are rare complications.
Coagulopathies are late complications of a long-standing severe cyanosis.
- Children with the acyanotic form of TOF gradually change to the cyanotic form by 1 to 3 years of age.
- In TOF with pulmonary atresia, most neonates die during the first 2 years of life; however, infants with extensive collaterals may survive for a long time, perhaps for > 15 years. Occasionally, patients with excessive collateral circulation develop hemoptysis during late childhood.

- In TOF with absent pulmonary valve, more than 75% of infants with severe pulmonary complications (e.g., atelectasis, pneumonia) die during infancy if treated only medically. Infants who survive infancy without serious pulmonary problems do well for 5 to 20 years.

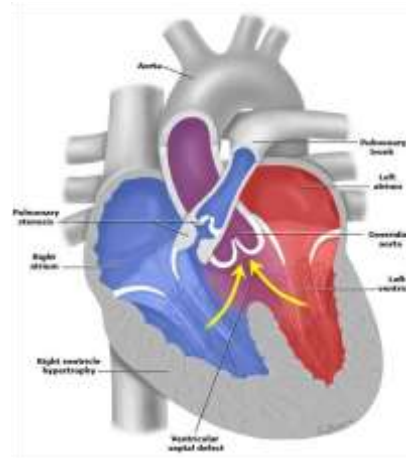


Figure 22-21: Tetralogy of Fallot.

Clinical Picture:

○ Symptoms:

Time of presentation and symptoms depend on the degree of RVOTO, which dictates the cyanosis severity:

- Neonates with TOF with pulmonary atresia are deeply cyanotic. The degree of cyanosis depends on whether the ductus is patent and how extensive the MAPCAs are.
- Patients with TOF with mild PS (acyanotic TOF) may be asymptomatic.

- TOF with absent pulmonary valve, Cyanosis disappears, and signs of CHF may develop, after the newborn period. Respiratory symptoms vary greatly; ranging from severe respiratory compromise, those with wheezing or frequent respiratory infection, and those with no respiratory symptoms at all.
- **Auscultation:**
 - Single S2 (the pulmonary component is too soft to be heard), and loud ejection systolic murmur at the ULSB (The murmur audible in cyanotic TOF originates from the RVOTO, not the VSD).
 - In TOF with pulmonary atresia, heart murmur cannot be heard. However, a continuous murmur representing PDA or collaterals may be audible.
 - In the acyanotic form, a long systolic murmur (resulting from VSD and infundibular stenosis) is audible along the entire LSB, and cyanosis is absent.
 - In TOF with absent pulmonary valve, A to-and-fro murmur (with “sawing-wood” sound) at the ULSB is characteristic (mild PS and free PR).
- **ECG:** RAD and RVH. In the acyanotic form, the QRS axis is normal.
- **Chest radiographs:**
 - In cyanotic TOF, it shows characteristic “boot-shaped heart” representing the prominent RV but relatively small main pulmonary arteries.
 - In acyanotic TOF, chest radiographs are indistinguishable from those of a small to moderate VSD.



Figure 22-22: Boot shaped heart.

Hypoxic Spell (also called cyanotic spell or “tet” spell):

- **Characterized by** paroxysm of: **(1)** hyperpnea (rapid and deep respiration), **(2)** irritability and prolonged crying, **(3)** increasing cyanosis, and **(4)** decreased intensity of the heart murmur.

A severe spell may lead to limpness, convulsion, cerebrovascular accident, or even death. It occurs in young infants, with peak incidence between 2 and 4 months of age.

- **Pathophysiology of hypoxic spell:** (\uparrow PS or \downarrow SVR \rightarrow \uparrow R-L shunt)

Lowering the systemic vascular resistance or increasing resistance at the RVOT will increase the R-L shunting, and this in turn stimulates the respiratory center to produce hyperpnea. Hyperpnea results in an increase in systemic venous return, which in turn increases the R-L shunt through the VSD, as there is an obstruction at the RVOT. A vicious circle becomes established.

- **Treatment of hypoxic spell:** Break the vicious circle by \uparrow preload **or** \downarrow the infundibular spasm:

- Pick up the infant and hold in a knee-chest position.
- Morphine sulfate (0.1 to 0.2 mg/kg) SC or IM suppresses the respiratory center and abolishes hyperpnea.
- Treat acidosis with sodium bicarbonate (1 mEq/kg). This reduces the respiratory center-stimulating effect.
- Oxygen inhalation has limited value, because the problem is a reduced PBF, not the ability to oxygenate.

- If not fully responsive to the above measures, the following may be tried:
 - (1) Ketamine (1-3 mg/kg) in a slow IV push, works well (by increasing the SVR and sedating the infant).
 - (2) Propranolol (0.01-0.25 mg/kg) in a slow IV push, reduces the heart rate and relieve infundibular spasm.

Diagnostic work-up:

- **Echocardiography** usually makes the diagnosis and quantitate the severity of TOF:
 - A perimembranous infundibular VSD and overriding aorta are imaged in the parasternal long-axis view.
 - Anatomy of the RVOT, the pulmonary valve, the pulmonary annulus, and the main PA and its branches is imaged in the parasternal short-axis and subcostal short-axis views.
 - Doppler studies estimate the pressure gradient across the RVOT obstruction.
 - Anomalous coronary artery distribution can be imaged in most cases by echo studies, primarily from the parasternal short- and long-axis views. The concern is to rule out any coronary artery crossing the RVOT.
 - Strain measurements are helpful in quantifying the degree of electromechanical dyssynchrony.
 - Associated anomalies such as ASD and persistence of the left SVC can be imaged.
- **CMR** is the method of choice for assessment of RV volume and function; PR; size, shape, and expansion of the PAs; infundibulum; the position of great vessels or conduits in relation to the sternum (resternotomy); and evaluation for residual shunt (Qp:Qs). Late gadolinium enhancement demonstrates fibrosis, the extent of which relates to other risk factors for VT and SCD. T1 mapping may have an emerging role.
- **CCT** provides information on coronary arteries (particularly important for the assessment of the spatial relationship with the RVOT prior to TPVI or surgery), the extent of conduit calcification (percutaneous valve anchoring), and the presence of major aortic pulmonary collaterals (MAPCAs).
- **CPET** assists timing of reintervention and provides prognostic information.
- **Holter monitoring, event recorder, and EP evaluation** are required for selected patients (high risk, suspected or clinical arrhythmia, and/or before RVOT reoperation). Inducible sustained VT carries prognostic value for clinical VT and SCD.

- **Cardiac catheterization** should be restricted to patients undergoing catheter-based interventions (i.e. relief of distal PA stenosis, transcatheter valve implantation) and when non-invasive evaluation is inconclusive.

Before surgery, coronary angiography may visualize the coronary arteries, which is important to assess the spatial relationship with the RVOT prior to TPVI.

Management:

- **Medical:**

- In TOF with pulmonary atresia, PGE1 infusion should be started as soon as the diagnosis is made or suspected to keep the ductus open for additional studies and to prepare for surgery.
- Hypoxic spells should be recognized and treated appropriately (as described before).
Oral propranolol may prevent hypoxic spells (due to its stabilizing action on peripheral vascular reactivity and thus prevent sudden fall of the SVR, rather than by prevention of RV outflow tract spasm).
- Detection and treatment of relative iron deficiency state. Anemic children are particularly prone to cerebrovascular accident.

- **Surgical:** The timing of surgery and initial surgical procedure (Early total repair or Palliative shunt followed by total repair) remains controversial.

- **Palliative procedures** are indicated to increase PBF. Modified Blalock-Taussig (MBT) shunt between the subclavian artery and the ipsilateral PA is the procedure of choice in small infants. Shunt operation may be chosen usually rather than primary repair in the following situations: Pulmonary atresia, hypoplastic PAs, Unfavorable coronary artery anatomy, and Infants younger than 3-4 months or weighing < 2.5 kg.

- **Total repair surgery:**

- A. Timing:**

- Symptomatic or cyanotic infants with favorable anatomy: at any time after 3 to 4 months of age.
- Asymptomatic and minimally cyanotic children: between 3 and 24 months.
- Mildly cyanotic infants who have had previous shunt surgery: at 1-2 years of age.

- In TOF with absent pulmonary valve: urgent surgery if symptomatic or at 3-6 months if asymptomatic.
- B. The procedure includes:** patch closure of the VSD, widening of the RVOT by resection of the infundibular muscle tissue, and usually placement of a fabric patch to widen the RVOT.
Surgery for TOF with anomalous LAD from RCA requires placement of a conduit between the RV and PA, which is usually performed after 1 year of age. A B-T shunt may be necessary initially to palliate the patient.

Indications for EP testing and ICDs:

- ICD should be implanted for secondary prevention of SCD (patients with cardiac arrest or sustained VT).
- In patients after repair of TOF with arrhythmia symptoms and positive PES, **or** a combination of other risk factors (including moderate RV or LV dysfunction, extensive RV scarring on CMR, QRS duration ≥ 180 ms and severe QRS fragmentation) and positive PES, ICD implantation should be considered.

Follow up recommendation:

All patients with TOF should have lifelong periodic cardiac follow up in most patients annually. All patients should have CMR at regular intervals, dependant on the pathology found.

Common complications in adulthood are:

- **Pulmonary Regurgitation (PR):** significant PR is almost always encountered following a transannular patch repair. PR is usually well tolerated for a decade or two. Severe chronic PR, however, eventually leads to symptomatic RV dilation and dysfunction. The severity of PR and its deleterious long-term effects are augmented by co-existing distal PA stenoses or PAH.
- **Valved conduits degeneration:** which requires conduit replacement at a later time. Valvular stenosis can be dilated with a balloon to reduce the pressure gradient but often results in a significant regurgitation.
- **Residual RVOTO** can occur at the infundibulum, at the level of the pulmonary valve and main pulmonary trunk, and into the branches of the left and right PA.

- **Residual VSD** can be due to partial patch dehiscence or failure of complete closure at the time of surgery; it may lead to LV volume overload.
- **Aortic complications** may occur many years after the initial surgical repair and include progressive aortic dilation and AR (rarely aortic dissection).
- **RV and LV dysfunction/heart failure:** RV dilation is usually due to residual longstanding free PR ± RVOTO. Significant TR may occur as a consequence of RV dilation, which begets more RV dilation. LV dilatation may result from longstanding palliative arterial shunts, residual VSDs, and/or AR. Both RV and LV dysfunction may be due to longstanding cyanosis before repair and/or inadequate myocardial protection during repair, adverse ventricular-ventricular interactions, electromechanical dyssynchrony, and coronary artery abnormalities.
- **Atrial/ventricular arrhythmias and SCD:** arrhythmias and sudden death are important late complications.
- **Endocarditis** can be encountered after both surgical and percutaneous PV replacement. Valve-containing prosthetics are an important independent risk factor for IE in the short- and long-term after implantation, whereas non-valve-containing prosthetics are a risk factor only during the first 6 months after implantation.

● **Intervention after TOF repair:**

| Table 22-16: ESC Recommendations for intervention after repair of tetralogy of Fallot: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>In patients with previous RVOT surgery (using homografts, bovine jugular vein grafts, bioprostheses/conduits), Transcatheter pulmonary valve implantation (TPVI) should be preferred if anatomically feasible.</i> | I | C |
| <i>PV replacement is recommended in symptomatic patients with severe PR (Regurgitant fraction by CMR > 30-40%) and/or at least moderate RVOTO (Peak velocity > 3 m/s).</i> | I | C |
| <i>PV replacement should be considered in asymptomatic patients with severe PR and/or RVOTO when one of the following criteria is present:</i> ○ <i>Decrease in objective exercise capacity.</i> | IIa | C |

| | | |
|---|------------|----------|
| <ul style="list-style-type: none"> ○ Progressive RV dilation to $RVESVi \geq 80 \text{ mL/m}^2$, and/or $RVEDVi \geq 160 \text{ mL/m}^2$, and/or progression of TR to at least moderate. ○ Progressive RV systolic dysfunction. ○ RVOTO with $RVSP > 80 \text{ mmHg}$. | | |
| VSD closure should be considered in patients with residual VSD and significant LV volume overload or if the patient is undergoing pulmonary valve surgery. | Ila | C |
| In patients with sustained VT who are undergoing surgical PV replacement or transcatheter valve insertion, pre-operative catheter mapping and transsection of VT-related anatomical isthmuses before or during the intervention should be considered. | Ila | C |
| EP evaluation, including programmed electrical stimulation, should be considered for risk stratification for SCD in patients with additional risk factors (LV/RV dysfunction; non-sustained, symptomatic VT; QRS duration $\geq 180 \text{ ms}$, extensive RV scarring on CMR). | Ila | C |
| ICD implantation should be considered in selected TOF patients with multiple risk factors for SCD, including: LV dysfunction, non-sustained, symptomatic VT, QRS duration $\geq 180 \text{ ms}$, extensive RV scarring on CMR, or inducible VT at programmed electrical stimulation. | Ila | C |
| Catheter ablation or concomitant surgical ablation for symptomatic monomorphic sustained VT may be considered in those with a preserved biventricular function as an alternative to ICD therapy, provided that the procedure is performed in highly experienced centres and that established ablation endpoints have been reached (e.g., non-inducibility, conduction block across ablation lines). | Ilb | C |

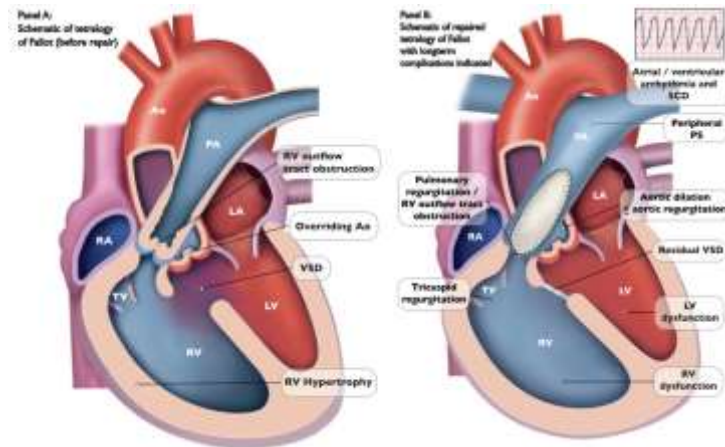


Figure 22-23: Management of repaired tetralogy of Fallot: long-term complications to address during follow-up. **Source:** 2020 ESC Guidelines for the management of adult congenital heart disease.

Ebstein anomaly

Pathophysiology:

- The septal and posterior leaflets of the tricuspid valve are displaced into the RV cavity, so that a portion of the RV is incorporated into the RA (atrialized RV), resulting in functional RV hypoplasia and TR. The anterior leaflet usually originates at the annular level but is enlarged and sail-like, while the septal and posterior leaflets are displaced towards the RV apex and often tethered to the endocardium.
- An interatrial communication is present, with resulting R-L atrial shunt (and varying degree of cyanosis).
- The RA is massively dilated and hypertrophied. The RV free wall is often thin. Fibrosis is present in the RV and LV free walls (which may cause ventricular dysfunction).

- The pathophysiology is characterized by systolic regurgitation of blood from the functional RV, across the TV, into the atrialized ventricle or RA, which tend to dilate. An interatrial connection permits a L-R shunt or, especially during exercise, a R-L shunt. Ebstein anomaly may result in a chronically low systemic cardiac output.
- The most frequently associated anomalies include: a shunt at the atrial level [secundum ASD or PFO] and (concealed) accessory pathways. Ebstein-like anomaly of the systemic TV is present in one-third of ccTGA.
- Hemodynamic changes depend on the severity of the TV dysfunction, the degree of atrialization of the RV, contractility of the remaining functional RV and the systemic ventricle, type and severity of concomitant anomalies, and arrhythmias.

Natural history:

- There is a great spectrum of Ebstein's anomaly, depending on the extent of the valvar displacement, with the most severe cases almost obliterating the functional cavity of the RV, leading to hydrops fetalis.
- Severe cases that survive to birth can be profoundly unwell post-natally with a hugely enlarged heart shadow occupying so much space that the lungs are small and underdeveloped. These cases have severe TR with a very small RV cavity and, if they survive, often have a functionally univentricular circulation.
- Conversely, the remainder of the spectrum of Ebstein can remain asymptomatic throughout childhood and tolerate the TR very well, some not presenting until adulthood.
- Associated ASD or accessory conduction pathways (leading to SVT) may be the presenting feature.

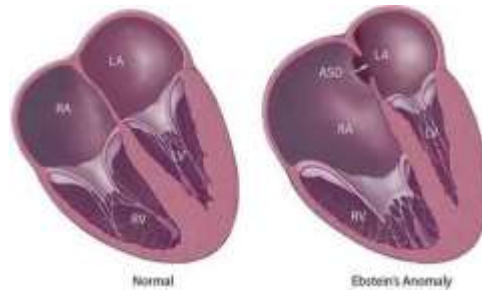


Figure 22-24: Ebstein anomaly of the tricuspid valve vs normal heart. There is a downward displacement of the tricuspid valve into the RV. An ASD is usually present.

Clinical Picture:

○ Manifestations:

- In severe cases, cyanosis and CHF develop in the first few days of life, with some subsequent improvement (with reduction of PVR).
- In milder cases, dyspnea, fatigue, and cyanosis on exertion may be present in childhood.
- **Auscultation:** The S2 is widely split. Characteristic triple or quadruple rhythm (Split S1, split S2, S3, and S4) is present. A soft regurgitant systolic murmur of TR is usually audible at the LLSB.
- **ECG:** RBBB and RAH. WPW preexcitation, SVT, and first-degree AV block are occasionally present.
- **Chest radiographs** may show extreme cardiomegaly, involving principally the RA, and decreased PVMs.

Diagnostic work-up:

- **Echocardiography** provides information on anatomy and function of the TV; apical distal displacement of the septal or posterior leaflet (in adults $\geq 8 \text{ mm/m}^2 \text{ BSA}$); size of the anterior leaflet; tethering of the septal or posterior TV leaflet on the septum or ventricular wall; size and function of the different cardiac sections (RA, atrialized ventricle, remaining functional RV, and LV); and RVOTO and associated lesions.

- **CMR** has value for prognostication, and for evaluation before and after surgery, as it offers unrestricted views for assessment and quantification of the dilated right heart, RV function, and TV function.

Management:

• Medical:

- In severely cyanotic newborns: mechanical ventilation, PGE1 infusion, inotropic agents, and correction of metabolic acidosis before proceeding with emergency surgery.
- Asymptomatic children with mild Ebstein's anomaly require only regular observation.
- Acute episodes of SVT may be treated most effectively with adenosine. Beta-blockers are the first-line preventive therapy. For patients with recurrent SVT, catheter ablation techniques have been successful.

• Surgical:

○ Indications of surgery:

- Critically ill neonates who show symptoms within the first week of life.
- Occurrence of severe or progressive cyanosis ($\text{SaO}_2 \leq 80\%$), polycythemia (Hb level ≥ 16 g/dL), or CHF.
- RVOT obstruction by redundant tricuspid valve.
- Severe activity limitation (i.e., NYHA class III or IV).
- History of paradoxical embolus.
- Repeated, life-threatening arrhythmias in patients with associated WPW syndrome.

○ Procedure:

- If good RV size and function: TV reconstruction with ASD closure.
- If poor RV size or function: staged Fontan operation (with ASD enlargement)
- If deeply cyanotic neonates: initial MBT is needed before BDG.
- During surgery, interruption of accessory pathway is recommended if recurrent SVT.

Table 22-17: ESC Recommendations for intervention in Adults with Ebstein anomaly:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Indications for surgery: | | |
| <i>Surgical repair is recommended in patients with severe TR and symptoms or objective deterioration of exercise capacity.</i> | I | C |
| <i>It is recommended that surgical repair is performed by a congenital surgeon with specific experience in Ebstein surgery.</i> | I | C |
| <i>If there is an indication for TV surgery, ASD/ PFO closure is recommended at the time of valve repair if it is expected to be haemodynamically tolerated.</i> | I | C |
| <i>Surgical repair should be considered regardless of symptoms in patients with progressive right heart dilation or reduction of RV systolic function.</i> | IIa | C |
| Indications for catheter intervention: | | |
| <i>In patients with symptomatic arrhythmias, or pre-excitation on the ECG, electrophysiologic testing followed by ablation therapy, if feasible, or surgical treatment of the arrhythmias in the case of planned heart surgery is recommended.</i> | I | C |
| <i>In adults with Ebstein, isolated device closure of ASD/PFO:</i> <i>-should be considered in case of systemic embolism, probably caused by paradoxical embolism,</i> <i>- may be considered if cyanosis (SaO₂ at rest < 90%) is the leading problem.</i> <i>but requires careful evaluation before intervention to exclude induction of RA pressure increase or fall in cardiac output.</i> | IIa | C |
| | IIb | C |
| | | |

Follow-up recommendations:

Regular follow-up (at least yearly) is required in all patients in specialized ACHD centres.

Typical post-operative residual anomalies to look for are persisting or new TR, the usual complications after valve replacement, failure of RV or LV, residual atrial shunts, arrhythmias, and higher-grade AV blocks.

Reintervention may become necessary for recurrent TR and failure of prosthetic valves.

Persistent Truncus Arteriosus

Pathophysiology:

- Only a single arterial trunk (with a truncal valve) leaves the heart and gives rise to the pulmonary, systemic, and coronary circulations. A large unrestrictive sub-arterial VSD is always present.
- Coronary artery abnormalities (stenotic coronary ostia, abnormal branching and course) are common, contributing to a high surgical mortality.
- The PBF is usually increased in type I, normal in types II and III, and decreased in type IV. As with other cyanotic CHDs, the level of systemic arterial oxygen saturation is directly related to the amount of PBF (With decreased PBF, cyanosis is notable. With increased PBF, cyanosis is minimal, but CHF may develop).
- DiGeorge syndrome with hypocalcemia is present in about 30% of patients. Interrupted aortic arch is seen in 13% (type B interruption between the left carotid and left subclavian arteries). A right aortic arch is present in 30% of patients.

Natural history:

Without surgery, most infants die of CHF within 6 to 12 months. Clinical improvement occurs if the infant develops PVOD. Truncal valve regurgitation, if present, worsens with time.

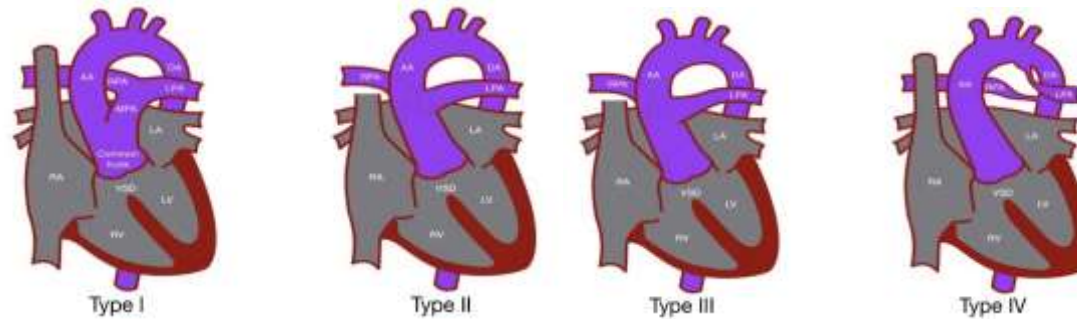


Figure 22-25: Collett and Edwards Classification of Truncus arteriosus. **Type I:** aorta and main pulmonary artery share a common arterial trunk. **Type II:** right and left pulmonary arteries arise separately from the posterior part of truncus. **Type III:** separate origins of the pulmonary arteries from the lateral aspect of the truncus. **Type IV:** neither pulmonary arterial branch arising from the common trunk with the lungs supplied by collaterals (pseudotruncus). **Source:** Radiopaedia.org.

Clinical Picture:

- **Manifestations:**
 - Cyanosis immediately after birth.
 - Signs of CHF may develop within several weeks (as the PVR falls, the left-to-right shunt through the VSD increases volume loading the heart).
 - Severe myocardial ischaemia which may cause sudden cardiac arrest (due to diastolic runoff to the low-resistance pulmonary vascular bed. This creates a steal of blood from the coronary arteries).
- **Auscultation:** regurgitant systolic murmur (suggestive of VSD) is present along the LSB. A high-pitched diastolic decrescendo murmur of truncal valve regurgitation is occasionally present. An apical diastolic rumble may be audible (PBF is large). Wide pulse pressure and bounding arterial pulses may be present.
- **ECG:** BVH (70% of patients); RVH or LVH is less common.

- **Chest radiographs:** cardiomegaly (biventricular and LA enlargement) and increased PVMs. A right aortic arch is seen in 30% of patients.

Diagnostic work-up:

- **Echocardiography:** The following three findings are diagnostic:
 - A large VSD is imaged directly under the truncal valve, similar to that seen in TOF.
 - A large, single great artery arises from the heart (i.e., truncus arteriosus). The type of persistent truncus arteriosus can be identified, and the size of the PAs can be determined. An artery, branching posteriorly from the truncus, is the PA.
 - The pulmonary valve cannot be imaged; only one semilunar valve (i.e., truncal valve) is imaged.
- **CT or MRI** may be necessary to evaluate arch anatomy or PA anatomy.

Management:

- **Medical:**

- Vigorous decongestive measures with diuretics and ACEIs are required before surgery.
- Pay attention to the following when DiGeorge syndrome is suspected or confirmed:
 - Serum Ca and Mg levels should be obtained.
 - Only irradiated blood product should be used.
 - Because of the thymus-based immune deficiency, treatment and prophylaxis against pneumococcal and streptococcal infection are important. Immunization with live vaccine should be avoided.

- **Surgical:**

- **Palliative procedures:** PA banding may be occasionally indicated in small infants with large PBF and CHF, but the mortality is high and the result not satisfactory.

- **Definitive Procedures:** Primary repair of the defect is recommended the first week of life. Complete repair was done via (i) separation of the pulmonary arteries from the truncus, (ii) repair of the resultant defect in the aorta, (iii) VSD closure with a patch, and (iv) restoration of RVOT continuity utilizing extra cardiac conduits.

Follow-up recommendations:

Follow-up every 4 to 12 months is required to detect late complications or problems.

- Truncal valve insufficiency may develop or progress.
- A small conduit needs to be replaced at 2-3 years of age.
- Calcification of the valve in the conduit may occur within 1 to 5 years.
- Ventricular arrhythmias may develop because of right ventriculotomy.

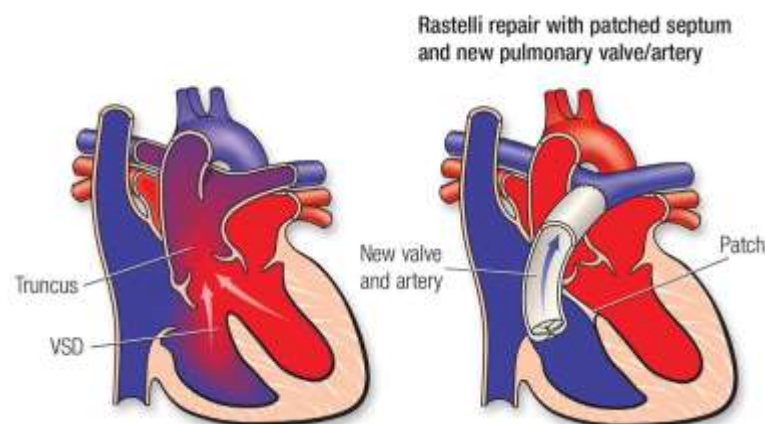


Figure 22-26: Rastelli repair of truncus arteriosus.

Total Anomalous Pulmonary Venous Return

Pathophysiology:

- The entire pulmonary venous return drains to the right side of the heart or the systemic venous system, usually via a common pulmonary venous confluence. An atrial communication (PFO or secundum ASD) is therefore essential to allow LV filling.
- **Depending on the drainage site of the pulmonary veins, the defects may be divided into:**
 1. **Supracardiac (50%):** a connection of the pulmonary venous confluence via a vertical vein into the SVC, the innominate vein or, rarely, the azygous vein.
 2. **Cardiac (20%):** The common PV drains into the coronary sinus, **or** directly into the RA.
 3. **Infracardiac (20%):** The pulmonary venous confluence lies posterior to the pericardium behind the heart and drains via a descending vertical vein, through the diaphragm, into the portal circulation or the IVC.
 4. **Mixed type (10%):** A combination of different types.
- The venous return from the pulmonary circulation drains to the right side of the heart (causing obligate mixing of the venous circulations and cyanosis), resulting in right heart volume loading, and the preload to the left side of the heart is entirely dependent on the atrial communication.
- If there is any obstruction to the pulmonary venous return into the systemic circulation, then there will be pulmonary venous congestion and pulmonary oedema. Obstruction is most commonly seen in infracardiac types where the draining vein is obstructed in its passage through the liver.
- Most patients with the infracardiac type and many patients with supracardiac and cardiac types of TAPVR have pulmonary hypertension secondary to obstruction of the pulmonary venous return.
- The level of systemic arterial oxygen saturation is proportional to the amount of PBF.

When there is no obstruction to PV return (as seen in most of the supracardiac and cardiac types), pulmonary venous return is large, and the systemic arterial blood is only minimally desaturated.

When there is obstruction to PV return (as seen in the infracardiac type), PV return is small, and the patient is severely cyanotic.

Natural history:

- b. If there is obstruction to pulmonary venous return, presentation is at birth with respiratory distress, cyanosis and collapse. Symptoms develop within 24 hours of birth, and death occurs without treatment in the first weeks of life.
- c. In the absence of pulmonary venous obstruction, patients present in early infancy with variable degrees of cyanosis and right heart volume overload.
- d. Patients with the infracardiac type rarely survive for longer than a few weeks without surgery. Most die before 2 months of age.

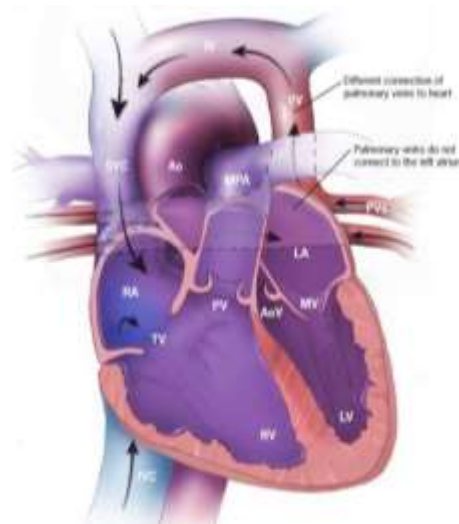


Figure 22-27: Supracardiac Total Anomalous Pulmonary Venous Return. Source: www.pedecho.org

Clinical Picture:

- Patients without PV obstruction:

- **Symptoms:** Growth retardation, mild cyanosis, and signs of CHF.
- **Auscultation:** S2 is widely split and fixed, and the P2 may be accentuated. Ejection systolic murmur is usually present at the ULSB (relative PS). A mid-diastolic rumble is present at the LLSB (relative TS).
- **ECG:** RAD, RVH (rsR' pattern in V1), and occasional RAH.
- **Chest radiographs** show moderate to marked cardiomegaly (involving RA and RV) with increased PVMs. A “snowman” sign is seen in older infants with the supracardiac type (usually after 4 months of age).
- **Patients with PV obstruction:**
 - **Symptoms:** Marked cyanosis and respiratory distress are present in the neonate.
 - **Auscultation:** A loud and single S2 and gallop rhythm are present. Heart murmur is usually absent. Pulmonary crackles may be audible.
 - **ECG:** RAD and RVH.
 - **Chest radiographs:** plethoric and congested lung fields with a relatively small heart shadow.
 - Patients with the infracardiac type rarely survive more than a few weeks without surgery.

Diagnostic Workup:

- **Echocardiography:**
 - e. A large RV with a compressed LV (i.e., relative hypoplasia of the LV) is the most striking initial finding.
 - f. An interatrial communication is usually present (PFO in 70% of patients, and secundum ASD occurs in 30%).
 - g. A large, common chamber (i.e., common pulmonary venous sinus) may be imaged posterior to the LA in the parasternal long-axis view.
 - h. Doppler studies reveal an increased flow velocity in the PA, an increased flow velocity or continuous flow at the site of the pulmonary venous drainage, and findings suggestive of pulmonary hypertension.
- **MRI or cardiac CT** can be used for diagnosis in cases of complex mixed type; the former is preferable because it does not use ionizing radiation.

Management:

- **In obstructed TAPVC:** emergent surgery, with surgical mortality rate of 20%.
- **In unobstructed TAPVC:** elective surgery before 6 months of age, with a mortality rate of 5-10%.

Follow-Up:

Follow-up is needed for possible late development of complication, which include:

- Paroxysms of pulmonary hypertension, which relate to small and poorly compliant left heart, with resulting cardiac failure and pulmonary edema, may require prolonged respiratory support postoperatively.
- Postoperative arrhythmias (usually atrial).
- PV obstruction may occur in about 10% of patients and requires reoperation. It can occur either at the anastomotic site or within the veins themselves.

Transposition of the Great Arteries

TGA is characterized by atrio-ventricular concordance and ventriculo-arterial discordance: the aorta originates from the morphological RV, the PA from the morphological LV.

TGA is called simple in the absence of associated congenital and anomalies; TGA is called complex in the presence of associated anomalies: VSD (45%), LVOTO (25%), and CoA (5%). Long-term outcome of complex TGA is, regardless of the type of surgical repair, worse than that of simple TGA.

Pathophysiology:

- The aorta (Ao) and the pulmonary artery are transposed, with the Ao arising anteriorly from the RV, and the PA arising posteriorly from the LV. The end result is complete separation of the two circuits, with hypoxemic blood circulating in the body and hyperoxemic blood circulating in the pulmonary circuit. The classic complete TGA is called d-transposition, in which the

aorta is located anteriorly and to the right of the PA; hence, d-TGA. When the transposed aorta lies to the left of the PA, it is called L-transposition.

- Defects that permit mixing of the two circulations, such as ASD, VSD, and PDA, are necessary for survival. A VSD is present in 40% of cases. In about 50% of the patients, no associated defects are present other than PFO, small ASD, or small PDA.
- LVOT obstruction (either dynamic or fixed) occurs in about 5% of patients without VSD. Dynamic LVOTO results from bowing of the interventricular septum to the left because of a high RV pressure. A combination of VSD and significant LVOTO (or PS) occurs in about 10% of all patients with D-TGA.
- In neonates with poor mixing of the two circulations, progressive hypoxia and acidosis result in early death, requiring an early intervention.

Natural history:

Natural history and prognosis depend on anatomy.

- i. Progressive hypoxia, acidosis, and heart failure result in death in the newborn period. Without surgical intervention, death occurs in 90% of patients before they reach 6 months of age.
- j. Infants with intact ventricular septum are the sickest group, but they demonstrate the most dramatic improvement following PGE1 infusion or the Rashkind balloon atrial septostomy.
- k. Infants with VSD or large PDA are the least cyanotic group but are most likely to develop CHF and PVOD (beginning as early as 3 or 4 months of age).
- l. Combination of VSD and PS allows longer survival without surgery because the pulmonary vascular bed is protected from developing pulmonary hypertension, but repair surgery carries a high risk.
- m. Cerebrovascular accident and progressive PVOD, particularly in infants with large VSD or PDA, are rare late complications.

Clinical Picture:

- **Symptoms:** Cyanosis since birth and signs of CHF develop in the newborn period. Severe arterial hypoxemia unresponsive to oxygen inhalation and acidosis are present in neonates with poor mixing. Hypoglycemia and hypocalcemia are occasionally present.
- **Auscultation:** nonspecific. The S2 is single and loud. No murmur is audible in infants with intact ventricular septum. When TGA is associated with VSD or PS, a systolic murmur of these defects may be audible.
- **ECG:** RAD and RVH. BVH may be present in infants with large VSD, PDA, or PS.
- **Chest radiographs:** cardiomegaly with increased pulmonary vascular markings. An egg-shaped cardiac silhouette with a narrow superior mediastinum is characteristic.
- **Echocardiography:** in the parasternal short-axis view, the great arteries appear as “double circles”. The PA is in the center of the heart, and the coronary arteries do not arise from this great artery. In the apical and subcostal five-chamber views, the PA (i.e., the artery that bifurcates) is seen to arise from the LV, and the aorta arises from the RV.

Management:

Stabilization before surgery:

- PGE1 infusion should be started to improve arterial oxygen saturation by reopening the ductus.
- If no adequate interatrial communication exists, cardiac catheterization and balloon atrial septostomy (i.e., the Rashkind procedure) are often carried out to have some flexibility in planning surgery.

Surgical approaches:

As a definitive surgery, the right- and left-sided structures are switched at the atrial level (Senning or mustard operation), at the ventricular level (Rastelli operation), or at the great artery level (arterial switch operation).

Strategy:

- **Simple TGA:**

Conditioned LV: arterial switch operation (ASO)

Unconditioned LV: First stage (PA banding + BT shunt) then ASO

○ **TGA + VSD:**

No PVOD: ASO

PVOD: palliative atrial switch (Senning or Mustard)

○ **TGA + LVOTO:**

Dynamic LVOTO: ASO

Fixed LVOTO: Commissurotomy + Atrial switch

○ **TGA + VSD + PS: (1)** BT shunt then Rastelli or **(2)** Nikaidoh operation or **(3)** REV operation

- **Arterial Switch Operation (ASO):** ASO is the procedure of choice. The coronaries are transplanted to the PA, and the proximal great arteries are connected to the distal end of the other great artery, resulting in an anatomic (not only physiologic) correction. For this procedure to be successful, the LV pressure should be near systemic levels at the time of surgery, and therefore should be performed before 3 weeks of age.

The operative mortality rate for neonates with simple TGA is down to around 2-3%.

- **Complications:** long-term complications are infrequent. The most common complications are:

- Coronary artery occlusion.
- Neo-aortic root dilatation, resulting in AR.
- Supravalvular PS at the anastomosis site and pulmonary branch stenosis (unilaterally or bilaterally), a consequence of the position of the pulmonary bifurcation anterior to the ascending aorta.
- LV dysfunction and ventricular arrhythmias are rare but may occur; both may be related to problems with the coronary arteries, which were reimplanted in the neo-aorta.
- Acute angle of the aortic arch, which may lead to functional obstruction and hypertension.

Table 22-18: ESC Recommendations for intervention in TGA after arterial switch operation:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|---|------------|----------|
| <i>Stenting or surgery (depending on substrate) is recommended for coronary artery stenosis causing ischemia.</i> | I | C |
| <i>Neo-aortic root surgery should be considered when the neo-aortic root is > 55 mm, providing average adult stature (for neo-aortic valve replacement for severe neo aortic AR see valvular heart disease guidelines with special considerations ⁽¹⁾).</i> | Ila | C |
| <i>Stenting should be considered for PA branch stenosis, regardless of symptoms, if > 50% diameter narrowing and RVSP > 50 mmHg and/or related reduced lung perfusion are present.</i> | Ila | C |

- **Atrial switch operation:** Intra-atrial repair surgeries (e.g., Senning or Mustard operation) are no longer performed, except in rare cases, because of undesirable late complications. These procedures reroute pulmonary and systemic venous returns at the atrial level with resulting physiologic correction. The pulmonary venous blood eventually goes to the aorta and the systemic venous blood goes to the PA. The Mustard operation uses a pericardial or a prosthetic baffle and the Senning operation uses the patient's own atrial septal flap and the RA free wall to redirect the venous returns.
- **Complications:** The most common complications are:
 - Systemic RV dysfunction and failure.
 - Secondary progressive TR (systemic AV valve).
 - Bradycardia and chronotropic incompetence due to loss of sinus rhythm; AV conduction is usually intact.
 - Supraventricular tachyarrhythmia, typically cavotricuspid isthmus-dependent flutter, followed by macro reentry circuit related to surgical incisions/scars; AF may occur at older age. High heart rates are often haemodynamically poorly tolerated because of the inability to increase preload, a consequence of the (restrictive) atrial baffles. Bradycardia due to SND can promote AT.
 - Ventricular tachyarrhythmias:
 - n. Primary polymorphic VT or VF due to poor ventricular function and heart failure-related mechanism, or monomorphic VT due to scar/incision/patch-related reentry in repaired complex TGA;

(1) It has to be taken into account that this is a reoperation and technically more difficult.

- o Secondary VT or VF, preceded by supraventricular tachycardia with rapid conduction and consecutive myocardial ischaemia due to the very low stroke volume associated with the SVT.
- o Baffle stenosis, either superior baffle (most common) or inferior baffle obstruction.
- o Baffle leakage, with either L-R shunt giving rise to pulmonary overflow or R-L shunting in the presence of distal flow obstruction, with cyanosis or paradoxical embolism.
- o Pulmonary veins/venous atrial obstruction, most often at the site where the pulmonary veins connect to the pulmonary venous atrium/RA.
- o LVOT obstruction can develop due to bulging of the interventricular septum towards the low-pressure subpulmonic LV, frequently associated with systolic anterior motion of the mitral valve.
- o PH can become manifest, sometimes decades after the atrial switch procedure; it is usually post-capillary, but PAH may be present too.
- o Death due to heart failure or sudden death, probably caused by arrhythmia.

| Table 22-19: ESC Recommendations for intervention in TGA after atrial switch operation: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Baffle leak or stenosis: | | |
| <i>In symptomatic patients with baffle leaks (symptoms due to L-R shunt or due to R-L shunt), stenting (covered) or device closure is recommended when technically feasible.</i> | I | C |
| <i>In asymptomatic patients with baffle leaks with substantial ventricular volume overload due to L-R shunt, stenting (covered) or device closure should be considered when technically feasible.</i> | IIa | C |
| <i>In patients with a baffle leak who require a PM/ICD, closure of the baffle leak with a covered stent should be considered, when technically feasible, prior to insertion of transvenous leads</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>In symptomatic patients with baffle stenosis, stenting is recommended when technically feasible.</i> | I | C |
| <i>In asymptomatic patients with baffle stenosis, stenting may be considered when technically feasible.</i> | IIb | C |
| <i>In symptomatic patients with baffle stenosis or leaks not amenable to catheter intervention, surgical repair is recommended.</i> | I | C |
| Pulmonary venous-atrium obstruction: | | |
| <i>In symptomatic patients with pulmonary venous-atrium obstruction, surgical repair (catheter intervention rarely possible) is recommended.</i> | I | C |
| Systemic (tricuspid) AV valve regurgitation: | | |
| <i>In patients with severe systemic (tricuspid) AV valve regurgitation, without significant ventricular systolic dysfunction (EF > 40%), valve repair or replacement should be considered, regardless of symptoms.</i> | IIa | C |
| <i>PA banding in adults, as LV training with subsequent arterial switch procedure, is not recommended.</i> | III | C |

- **Rastelli operation:** In patients with VSD and severe PS, redirection of the pulmonary and systemic venous blood is carried out at the ventricular level. The LV is directed to the aorta by creating an intraventricular tunnel between the VSD and the aortic valve. A valved conduit or a homograft is placed between the RV and the PA. This procedure is less popular because of late complications (10%) and a high surgical mortality rate (29%).
Two alternative procedures are now available: REV procedure (intraventricular baffle to direct LV output to the aorta and direct RV-to-PA reconstruction) and Nikaidoh procedure (the aortic root is translocated to the pulmonary position).
- **Complications:** Common complications are:
 - Stenosis or regurgitation of the valved conduit between the RV and the PA.

- LVOT obstruction (i.e., obstruction of the flow from the LV to the aorta).
- Residual VSD.
- AR.
- LV dysfunction.
- Arrhythmias, both ventricular and supraventricular.
- Endocarditis of the valved conduit.
- Death, either sudden (arrhythmia) or due to heart failure.

Follow-Up:

All patients with TGA should be seen at least annually.

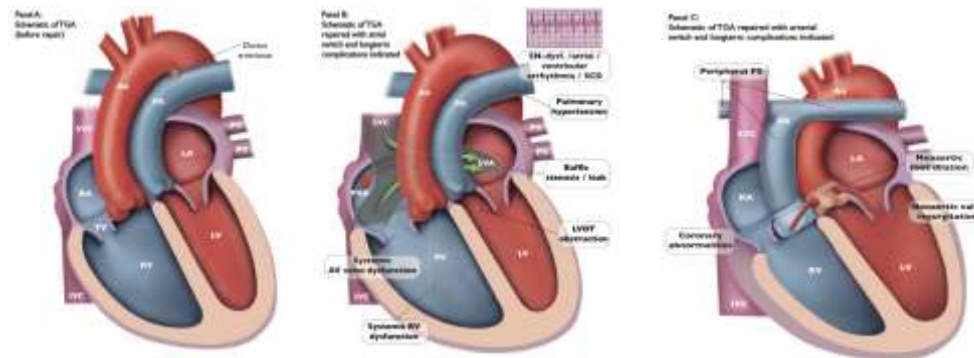


Figure 22-28: Management of transposition of the great arteries: long-term complications to address during follow-up.

Source: 2020 ESC Guidelines for the management of adult congenital heart disease.

Congenitally corrected TGA

Pathophysiology:

- Visceroatrial relationship is normal, but there is ventricular inversion (V-A and A-V discordance).
The RA on the right of the LA and receives systemic venous blood. The RA empties into the anatomic LV through the mitral valve, and the LA empties into the RV through the tricuspid valve. For this to occur, the LV lies to the right of the RV (i.e., ventricular inversion).
The great arteries are transposed, with the aorta arising from the RV and the PA arising from the LV. The aorta lies to the left of and anterior to the PA (hence L-TGA). The final result is a functional correction in that oxygenated blood coming into the LA goes to the aorta.
- Theoretically, no functional abnormalities exist, but unfortunately most cases are complicated by associated intracardiac defects, AV conduction disturbances, and arrhythmias (mostly supraventricular).
- **Associated cardiac defects** include: VSD (occurring in 80%), PS (in 50%), and hypoplastic ventricle.
- Abnormal base-apex orientation, especially dextrocardia (apex of the heart pointed to the right), is common (20%).
- The coronary arteries show a mirror-image distribution. The right-sided coronary artery supplies the LAD and LCx; the left-sided coronary artery resembles a right coronary artery (Essentially, coronary arteries follow the ventricles).
- The position of the AV node (sometimes multiple AV nodes), and the course of the bundle of His, are often abnormal and lead to AV conduction abnormalities (may be progressive). The anterior and lateral displacement of a fragile His bundle is important to recognize during EP studies and catheter interventions.

Natural history:

The clinical course is determined by the presence of associated defects and complications.

- p. Some palliative surgeries are usually needed in infancy when L-TGA is associated with other defects (e.g., PA banding for a large VSD **or** a systemic-to-PA shunt for severe PS). Without these procedures, 20-30% of patients die in the first year. CHF is the most common cause of death.
- q. Regurgitation of the systemic AV valve (anatomic tricuspid valve) develops in about 30% of patients.
- r. Progressive AV conduction disturbances (including CHB) may occur in up to 30% of cases. These disturbances occur more often in patients without VSD than in those with VSD.
- s. Occasional adult patients without major associated defects are asymptomatic.

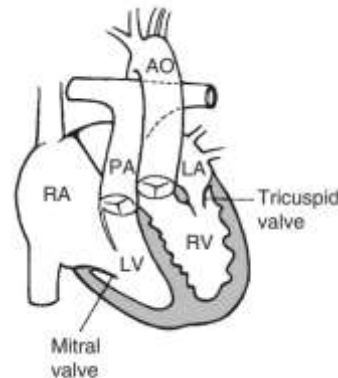


Figure 22-29: Diagram of congenitally corrected TGA (L-TGA). Source: Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Clinical Picture:

- o **Manifestations:** Presentation depends entirely on the associated lesions. Patients with a large VSD may present in heart failure, those with pulmonary stenosis or atresia will be cyanosed and those with arch hypoplasia may present with circulatory collapse. Patients without associated defects are asymptomatic.

- **Auscultation:** The S2 is single and loud. Holosystolic murmur along the LLSB may indicate a VSD or the systemic AV valve (tricuspid) regurgitation. Ejection systolic murmur at the ULSB or URSB may indicate PS.
- **ECG:** Characteristic findings are the absence of Q waves in V5 and V6. Varying degrees of AV block (including CHB) may be present. Atrial and/or ventricular hypertrophy may be present in complicated cases.
- **Chest radiographs:** show a characteristic straight left upper cardiac border (formed by the ascending aorta). Cardiomegaly and increased PVMs suggest associated VSD. Dextrocardia is frequent (50%).
- TR develops in about 30% of patients. Progressive AV conduction disturbances, including complete heart block (up to 30%), may occur.

Diagnostic work-up:

- **Echocardiography:** with use of the segmental approach, the diagnosis of L-TGA can be made easily, and associated anomalies can be detected and quantitated.
 - The parasternal long-axis view is obtained from a more vertical and leftward scan than with a normal heart. The aorta, which arises from the posterior ventricle, is not in fibrous continuity with the mitral valve.
 - In the parasternal short-axis scan, a “double circle” of the semilunar valves is imaged. The posterior circle is the PA without demonstrable coronary arteries. The aorta is anterior to and left of the PA.
 - In the apical and subcostal four-chamber views, the LA is connected to the tricuspid valve (which has a more apical attachment to the ventricular septum than the other), and the RA is connected to the mitral valve. The anterior artery (aorta) arises from the left-sided morphologic RV.
 - The situs solitus of the atria is confirmed by the drainage of systemic veins to the right-sided atrium and the drainage of pulmonary veins to the left-sided atrium.
- **CMR** provides intracardiac and great vessel anatomy and is indicated for quantification of ventricular volumes, mass, and EF, especially since echocardiographic assessment of systolic function in systemic RVs is difficult and less reliable.

- **Holter monitoring**, event recorder, and EP testing may be indicated for detection of arrhythmias, progressive AV block, and for risk assessment for SCD.
- **Cardiac catheterization** is indicated when non-invasive testing is inconclusive, or PH requires evaluation.

Management:

- **Medical:** There are no data to support that ACEIs/ARBs, beta blockers or aldosterone antagonists improve outcomes or prevent heart failure. However, these medications in addition to diuretics may provide relief of symptoms.
- **Surgical:**
 - **Initial treatment:** this will depend on the mode of presentation and the associated lesions:
 - Neonates with arch hypoplasia/coarctation require resuscitation and urgent surgical repair.
 - If there is associated VSD, then a PA band may be placed at the same time to balance the circulation.
 - Patients with pulmonary stenosis or atresia require initial palliation with a BT shunt.
 - **Definitive Procedures:** There are two major approaches to surgical management of L-TGA:
 - **Classic (physiological) Repair:** Physiological repair consists of the correction of associated lesions, including VSD closure, tricuspid valve repair and RV outflow obstruction relief (Anatomical RV remains as the systemic ventricle, so RV failure may develop overtime).
 - **Anatomic Repair:** anatomical repairs aim for atrial switch (Senning or Mustard procedures) in addition to an arterial switch or a Rastelli procedure (RV-PA conduit). Anatomic repair makes the anatomic LV the systemic ventricle, which may reduce the likelihood of TR and RV failure. This repair is associated with a prolonged aortic clamping time and a high early mortality, but this procedure is a better choice for patients with TR or RV dysfunction.

Table 22-20: ESC Recommendations for intervention in congenitally corrected TGA:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In symptomatic patients with severe TR and preserved or mildly impaired systemic RV systolic function (EF > 40%), TV replacement is indicated (Repair is rarely feasible).</i> | I | C |

| | | |
|--|------------|----------|
| <i>In asymptomatic patients with severe TR and progressive systemic RV dilatation and/or mildly impaired systemic RV systolic function (EF > 40%), TV replacement should be considered.</i> | Ila | C |
| <i>Biventricular pacing should be considered in case of complete AV block or > 40% ventricular pacing requirement.</i> | Ila | C |
| <i>In symptomatic patients with severe TR and more than mildly reduced systemic RV systolic function (EF ≤ 40%), TV replacement may be considered.</i> | Ilb | C |

Follow-up recommendations:

Patients with ccTGA need lifelong follow-up in a specialized centre at annual intervals, particularly because of conduction disturbances and subaortic ventricular and subaortic AV valve dysfunction.

Late complications are:

- Systemic RV dysfunction and failure.
- Progressive TR (systemic AV valve).
- LVOT Obstruction.
- Complete AV block (2% loss of AV conduction per year); it is more common after VSD repair and/or TV replacement and may occur during pregnancy.
- VTs (extremely rare).

Right ventricular to pulmonary artery conduit

- Conduits establish the continuity between the RV and the PA in complex defects when there is discontinuity between the RV and PA. Those lesions include:
 - Absent RVOT (e.g., pulmonary atresia, truncus arteriosus).
 - Unsuitable RVOT (e.g., D-TGA + VSD + PS **or** complicated DORV **or** L-TGA + PS).

- Iatrogenic: e.g., Ross operation.
- Types of conduits include valved [pulmonary or aortic homograft, bioprosthetic valves, bovine jugular vein conduits (Contegra)] and non-valved conduits.
- There is no ideal conduit. Limited durability implicates early reoperation.
- Predictors for conduit failure are: sterilization/preservation process, smaller conduit, conduit type, younger age at implantation, PA stenosis, and diagnosis of transposition.
- Freedom from reoperation for conduit failure at 20 years was reported at 32% and 40%.

Diagnostic work-up:

- **Echocardiography** is the first-line diagnostic tool providing size, shape, and function of both ventricles, PR, TR, and associated lesions. Gradients across the conduit may be difficult to measure and unreliable. RV pressure derived from TR velocity should be used to assess conduit stenoses.
- **CMR** is used to quantify conduit stenosis and/or regurgitation, RV volumes and mass, and to assess PAs.
- **CMR/CCT** is helpful for coronary artery anatomy and proximity of the RV/conduit, and other structures to the retro sternum.
- **Catheterization** with haemodynamic assessment is always required if intervention is considered. Angiography provides information on the level of stenosis, peripheral PA stenoses, and coronary anatomy (anomalies/abnormal course).

Indications for intervention:

| Table 22-21: ESC Recommendations for intervention in RV to PA conduits: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Symptomatic patients with RVSP > 60 mmHg (may be lower in case of reduced flow) and/or severe PR (Regurgitant fraction by CMR > 30-40%) should undergo intervention with preference for catheter intervention (TPVI) if anatomically feasible. | I | C |

Asymptomatic patients with severe RVOTO and/or severe PR should be considered for intervention, preferably catheter intervention (TPVI) if anatomically feasible, when at least one of the following criteria is present:

- *Decrease in objective exercise capacity (CPET).*
- *Progressive RV dilation to $RVESVi \geq 80 \text{ mL/m}^2$, and/or $RVEDVi \geq 160 \text{ mL/m}^2$, and/or progression of TR to at least moderate.*
- *Progressive RV systolic dysfunction.*
- *RVSP > 80 mmHg*

IIa

C

Follow-up recommendations:

Regular follow-up in a specialized ACHD centre at least every year is recommended. Special attention should be given to exercise capacity (CPET), RVSP (conduit gradient), RV function, TR, and arrhythmias.

Double-Outlet Right Ventricle (DORV)

The term 'DORV' means that there is a VSD and that both the great arteries are (predominantly) arising from the RV. The aorta often overrides the VSD, but at least 50% of the aorta must be committed to the RV in order to classify as a DORV.

Pathophysiology:

- Both the aorta and the PA arise side by side from the RV. The only outlet from the LV is a large VSD. The aortic and pulmonary valves are at the same level. Conus septum is present between the aorta and the PA. The subaortic and subpulmonary coni separate the aortic and pulmonary valves from the tricuspid and mitral valves, respectively. This means that there is no fibrous continuity between the semilunar valves and the AV valves.
- **DORV may be subdivided according to the position of the VSD and further by the presence of PS/RVOTO:**

- **Subaortic VSD and no PS** (most common type, occurring in 50-70% of the patients): oxygenated blood from the LV is directed to the aorta, and desaturated systemic venous blood is directed to the pulmonary artery, producing mild or no cyanosis. Clinical pictures resemble those of a large **VSD** with pulmonary hypertension and CHF.
- **Subaortic VSD with PS (Fallot type)**: Even though the VSD is subaortic, in the presence of PS/RVOTO, some desaturated blood goes to the aorta. This causes cyanosis and a decrease in PBF. The clinical pictures resemble **TOF**.
- **Subpulmonary VSD (Taussig-Bing anomaly)**: oxygenated blood from the LV is directed to the PA, and desaturated blood from the systemic vein is directed to the aorta, producing severe cyanosis. The clinical pictures resemble **TGA**.
- **In doubly committed VSD or Non committed VSD**: mild cyanosis is present and the PBF is increased.

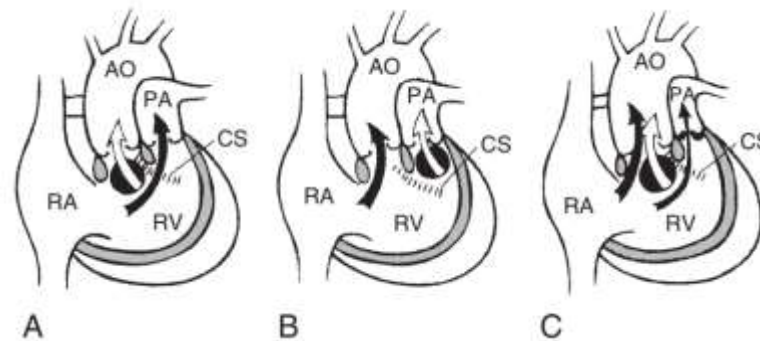


Figure 22-30: Three representative types of DORV, viewed with the RV free wall removed. (A) Subaortic VSD. (B) Subpulmonary VSD (Taussig-Bing anomaly). (C) Subaortic VSD with PS. **Source:** Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Natural history:

- Infants without PS may develop severe CHF and later pulmonary vascular obstructive disease if left untreated. Spontaneous closure of VSD, which is fatal, is rare.
- When PS is present, complications common to cyanotic CHDs (e.g., polycythemia, cerebrovascular accident) may develop.

- In patients with the Taussig-Bing malformation, severe pulmonary vascular obstructive disease develops early in life, as seen in patients with D-TGA.

Clinical Picture:

- **Subaortic VSD without PS:**

- Physical findings resemble those of a large VSD (i.e CHF and failure to thrive).
- ECG often resembles that of ECD (“superior” QRS axis, LAH, RVH, or BVH and occasional 1st AV block).
- Chest radiographs show cardiomegaly with increased PVMs and prominent MPA.

- **Subaortic VSD with PS (Fallot type):**

- Physical findings resemble those of TOF.
- ECG shows RAD, RAH, and RVH or RBBB.
- Chest radiographs show normal heart size (with upturned apex) and decreased PVMs.

- **Subpulmonary VSD (Taussig-Bing malformation):**

- Physical findings resemble those of TGA with severe cyanosis in newborn infants.
- ECG shows RAD, RAH, and RVH. First-degree AV block is frequently present.
- Chest radiographs show cardiomegaly with increased pulmonary vascular markings and prominent MPA.

Diagnostic work-up:

Echocardiography: Four diagnostic signs of DORV are: **(1)** the presence of a large subaortic or subpulmonary VSD, **(2)** the origin of both great arteries from the anterior RV, **(3)** the absence of LV outflow other than the VSD, and **(4)** the absence of normal aortic-mitral continuity.

- In the parasternal long-axis view, all four diagnostic features of DORV are imaged. Typical subaortic or subpulmonary VSD can be demonstrated in this view. No great artery is seen to arise from the posterior ventricle (LV). The great arteries arising from the anterior ventricle (RV) are seen in parallel orientation.

- In the parasternal short-axis view, a double circle, rather than the normal circle and sausage appearance of the great arteries, is seen. The aorta to the right or the aorta is anterior and slightly to the right of PA.
- The size and position of the VSD should be determined in relation to the great arteries:
 - Typical subpulmonary or subaortic VSD can be demonstrated by parasternal long-axis.
 - In the subcostal four-chamber view, the subaortic VSD is located to the right of the conus septum just beneath the aortic valve. The subpulmonary VSD is located to the left of the conus septum just beneath the pulmonary valve.
 - Doubly committed VSD is recognized in the parasternal or the apical long-axis view.
 - Non-committed VSDs are best seen in the apical four-chamber view.



Figure 22-31: Fallot-type DORV. The VSD is subaortic. Notice that the aorta is not fully arising from the RV and that there is a subpulmonary obstruction (full arrow). There is a mitral-aortic discontinuity (*). **Source:** E.M. da Cruz et al. (eds.), Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care, 2003 DOI 10.1007/978-1-4471-4619-3_49.

Management:

- **Medical:** Medical treatment of CHF if present.
- **Surgical:**

- **For non-committed or multiple VSDs** (with large PBF and CHF):
 - **Palliative procedure:** a PA banding is occasionally performed.
 - **Corrective procedure:** When possible, an intraventricular tunnel procedure (between inlet VSD and the aorta) is preferred (performed at age 2 to 3 years with a high mortality of 30% to 40%). PA banding is usually needed in infancy to control CHF.
- **For subaortic VSD and PS** (Fallot type):
 - **Palliative procedure:** a B-T shunt or RVOT stent may be indicated to increase pulmonary blood flow.
 - **Corrective procedure:** There are three surgical options: **(1)** an intraventricular VSD-to-aorta tunnel plus RV-to-PA homograft valved conduit at 6 months to 2 years of age, **(2)** REV procedure, or **(3)** Nikaidoh procedure.
- **For subpulmonary VSD (Taussig-Bing malformation):**
 - **Palliative procedure:** enlarging the ASD by the balloon or blade atrial septectomy is important for decompression of the LA and better mixing of pulmonary and systemic venous blood.
 - **Corrective procedure:** There are four possible surgical approaches: **(1)** an intraventricular tunnel between the VSD and the PA (turning it into TGA), plus the arterial switch operation during the first month of life (surgical mortality of 10% to 15%); **(2)** as in (1) plus the Senning operation (less desirable; surgical mortality above 40%); **(3)** an intraventricular tunnel between the subpulmonary VSD and the aorta is desirable if technically feasible (mortality of 15%); and **(4)** creation of a VSD-to-PA tunnel, followed by Damus-Kaye-Stansel operation and RV-to-PA conduit.

Follow-up recommendations:

Longterm follow-up at 6- to 12-month intervals is necessary to detect late complications (such as the need to reoperate and ventricular arrhythmias).

Univentricular heart

The term 'UVH' summarizes a variety of malformations where either the RV or LV is missing or, if present, is hypoplastic and thus not amenable for biventricular repair.

Pathophysiology:

- Both AV valves are connected to a main, single ventricular chamber (i.e., double-inlet ventricle), and the main chamber is in turn connected to a rudimentary chamber through bulboventricular foramen (BVF).
In about 80% of cases, the main ventricular chamber has anatomic characteristics of the LV (i.e., double-inlet LV). Occasionally, the main chamber has anatomic characteristics of the RV (i.e., double-inlet RV).
- Rarely does the ventricle have an intermediate trabecular pattern without a rudimentary chamber (i.e., common ventricle).
- Because there is a complete mixing in the single ventricle, the systemic arterial saturation is determined primarily by the amount of PBF:
 - **With PS**, PBF is decreased, and cyanosis is present (with $\text{SaO}_2 < 85\%$). With pulmonary atresia, cyanosis is intense at birth.
 - **When the pulmonary valve is not stenotic**, the PBF is large, and signs of CHF develop within days or weeks without cyanosis; SaO_2 is nearly 90%. When left untreated, pulmonary overcirculation can lead to pulmonary hypertension, which jeopardizes future Fontan operation.
- An obstructed BVF may either occur naturally with growth or develop after PA banding (for unknown reasons). The occurrence of an obstructed BVF has a profound hemodynamic effect, as well as major surgical implications in patients with the aorta arising from the anterior rudimentary chamber. The obstruction increases PBF and decreases systemic perfusion.

Natural history:

- **In patients without PS:** Without surgery, about 50% of these patients die before reaching 1 year of age. The remainder of the patients with increased PBF develops pulmonary vascular obstructive disease after the first year of life with clinical improvement of CHF.

- **In patients with associated PS:** cyanosis increases if PS worsens.
- If the aorta arises from the rudimentary chamber, the BVF is often small or becomes obstructed. This results in increased PBF and decreased systemic perfusion.
- Progressive AV valve regurgitation is poorly tolerated.
- Complete heart block develops in about 12% of patients.
- The cause of death can be CHF, arrhythmias, or sudden death.

Univentricular heart includes the following malformations:

| Dominant Left ventricle | Dominant Right ventricle |
|---|---|
| <ul style="list-style-type: none"> - Tricuspid atresia - Double-inlet left ventricle (DILV) - Pulmonary atresia with intact septum - Unbalanced AVSD (dominant left) - Transposition/VSD with small RV | <ul style="list-style-type: none"> - Hypoplastic left heart syndrome - DORV with mitral atresia - Unbalanced AVSD (dominant right) |

N.B: A functionally single ventricle is the only congenital heart disease with cyanosis yet isolated LVH on ECG, rather than RVH.

Diagnostic work-up:

- **Echocardiography** is the key diagnostic technique, providing information on anatomy and monitoring of cardiac function during follow-up. The most important diagnostic sign of single ventricle is the presence of a *single ventricular chamber into which two AV valves open*. UVHs are always complex and can present with a wide range of abnormalities in situs, orientation, and connections.

Fundamental TTE parameters/issues/items in the diagnosis of UVHs are:

- Abdominal and atrial situs.
- Position of the heart in the chest and position of the apex.

- Veno-atrial, AV, and ventriculo-arterial connections.
- Exact anatomy of the ventriculo-arterial connection and its functional status has to be assessed, with special focus on obstruction towards the aorta or pulmonary vascular bed.
- AV valve function should be evaluated, with special focus on regurgitation.
- Ventricular function/hypertrophy.
- ASD/VSD type, size, number, location.
- Ascending aorta, aortic arch, and descending aorta; detect/ exclude coarctation.
- PAs common trunk, branches, and sources of pulmonary blood supply.
- Visualization of shunts (BlalockTaussig, Waterston, etc.).
- **CMR** is the imaging modality of choice for extracardiac anatomy, including veno-atrial and ventriculo-arterial connections (CCT is an alternative). CMR is also the method of choice for quantification of ventricular volumes, EF, and relative distribution of blood flow in the left and right lungs.
- **Cardiac catheterization** is required when intervention is considered for hemodynamic assessment, in particular PAP and transpulmonary gradient (PVR is often difficult to assess in this setting). It is mandatory when patients are evaluated for a Fontan operation. Evaluation of systemic-to-PA or Glenn shunts and their sequelae (stenosis of the pulmonary branches) and other vascular anomalies (arteriovenous collateral vessels, fistulas, etc.) may also require catheterization.

Management:

Idea:

- Most infants require one or more palliative procedures before Fontan operation, the definitive surgery, can be performed. These palliative surgical procedures are aimed at producing ideal candidates for future Fontan.
- Ideal candidates for Fontan are those who have normal LV function and low PVR:
 - Normal LV function results from prevention of excessive volume or pressure loading of the LV by:
 - Preventing excessive volume load by using a relatively small systemic-to-pulmonary shunt.

- Avoiding ventricular hypertrophy (e.g., by relieving the LVOT obstruction)
- Low pulmonary vascular resistance may result from:
 - Providing adequate PBF which promote the growth of PA branches (with resulting increase in the cross-sectional area of the pulmonary vascular bed).
 - Protecting pulmonary vascular bed from overflow or pressure overload (by PA band when PBF is increased).

Strategy:

• Medical:

- Intravenous PGE1 infusion is indicated in cyanotic neonates to maintain the patency of the ductus. The balloon atrial septostomy (Rashkind procedure) may be performed to improve the R-L atrial shunt.
- Infants with VSD of adequate size and normal PBF need to be followed closely for decreasing oxygen saturation which may be caused by reduction in the size of the VSD.

• Surgical:

- **Initial surgical palliative procedures:** The purpose of the first-stage operation is to make patients acceptable candidates for bidirectional Glenn or hemi-Fontan operation.
- **No PS:** In patients with no PS and large PBF with resulting CHF and pulmonary edema, **PA banding** may be done. The major risk factor for the banding is the presence or development of an obstructed BVF. Therefore, PA banding is performed only when the BVF is normal or unobstructed.
- **No PS + obstructed BVF:** the Damus-Kaye-Stansel (**DKS**) operation is performed rather than PA banding. The operation involves a PA-to-aorta anastomosis, which is accomplished by transection of the main PA and anastomosis of the proximal PA to the ascending aorta. This operation is combined with a right-sided BT shunt.
- **PS or pulmonary atresia:** a **BT shunt** is necessary to improve cyanosis. Shunt to the right PA is preferable because any distortion of the RPA can be incorporated later in the Fontan anastomosis.
- **PS + obstructed BVF: enlargement of the BVF** by a transaortic approach and without cardiopulmonary bypass may be performed. The surgical mortality rate is about 15%.

○ **Second-stage surgical palliative procedures:**

- Bidirectional Glenn operation is carried out between the age of 3 month and 6 months, before proceeding with the Fontan operation. Alternatively, the hemi-Fontan procedure can be performed.
- After the second-stage surgical procedure, the child needs to be followed up with attention to the SaO₂.

○ **Definitive (Fontan) procedures:** The Fontan-type operation is performed at 2 to 5 years of age. The surgical mortality rate of the Fontan-type operation has been reduced to 5-10%.

| Table 22-22: ESC recommendations for intervention in adults with univentricular heart: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>It is recommended that adults with unoperated or palliated UVHs undergo careful evaluation in specialized centres, including multimodality imaging as well as invasive work-up to decide whether they may benefit from surgical or interventional procedures.</i> | I | C |
| <i>Only well-selected symptomatic cyanotic patients should be considered candidates for a Fontan circulation after careful evaluation [low PVR, adequate function of the AV valve(s), preserved ventricular function].</i> | IIa | C |
| <i>Patients with increased pulmonary blood flow unlikely at adult age should be considered for PA banding or tightening of a previously placed band.</i> | IIa | C |
| <i>Patients with severe cyanosis and decreased pulmonary blood flow, but without elevated PVR or PAP, should be considered for a bidirectional Glenn shunt.</i> | IIa | C |
| <i>Patients with severe cyanosis and decreased pulmonary blood flow not suitable for a Glenn shunt may be considered for a systemic-to-PA shunt.</i> | IIb | C |
| <i>Heart transplantation and heart-lung transplantation should be considered when there is no conventional surgical option in patients with poor clinical status.</i> | IIa | C |

Tricuspid Atresia

Pathophysiology:

- The tricuspid valve is absent, and the RV and PA are hypoplastic, with decreased PBF. The great arteries are transposed in 30% and normally related in 70% of the cases. Associated defects such as ASD, VSD, or PDA are necessary for survival.
- In patients with normally related great arteries (most common), a small VSD and PS (with hypoplasia of the PAs) are present. In patients with transposed great arteries, the pulmonary valve is normal sized.
- All systemic venous return is shunted from the RA to the LA, with resulting dilation and hypertrophy of the RA. The LA and LV are large because they handle both systemic and pulmonary venous returns. The level of arterial saturation is positively related to the level of PBF.
- COA or interrupted aortic arch is a frequently associated anomaly, more commonly in cases with TGA.

Natural history:

- Few infants survive beyond 6 months of life without surgical palliation. Occasional patients with increased PBF develop pulmonary hypertension and LV failure, which preclude successful Fontan operation.
- For patients who survive into their second decade of life without Fontan-type operation, the chronic volume overload of the LV usually results in LV systolic dysfunction, which is a known risk factor for Fontan operation (The Fontan procedure should be performed before LV dysfunction develops).

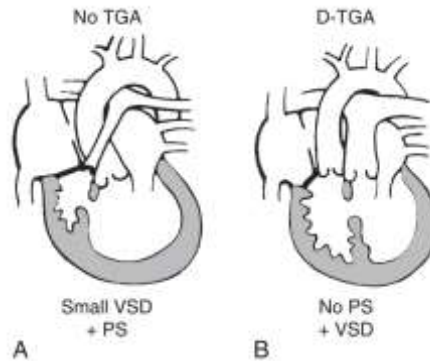


Figure 22-32: The two most common types of tricuspid atresia. (A) In about 50% of patients, the great arteries are normally related and a small VSD and PS are present. **(B)** When the great arteries are transposed (about 20% of all cases), a VSD is usually present without PS. **Source:** Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Clinical Picture:

- **Manifestations:** Severe cyanosis, tachypnea, and poor feeding are usual.
- **Auscultation:** S2 is single. Systolic regurgitant murmur of VSD is usually present at the LLSB. A continuous murmur of PDA is occasionally audible.
- **ECG:** superior axis (in most patients without TGA and 50% of patients with TGA), RAH or BAH, and LVH.
- **Chest radiographs** show normal or slightly increased heart size and decreased PVMs. A boot-shaped heart with a concave MPA segment may be seen. In infants with TGA, PVMs may be increased.

Diagnostic Workup:

- **Echocardiography** shows absence of the tricuspid orifice, large LV, diminutive RV, and ASD. The presence or absence of TGA, VSD, PDA, and COA is also imaged. The size of the VSD, the presence and severity of PS, and the presence of TGA should all be investigated. Patients with TGA should be examined for possible subaortic stenosis and COA.

- **Cardiac catheterization** with atrial septostomy is indicated when atrial communication is inadequate. Cardiac catheterization is generally recommended before any Fontan-type operation to gain information on the PA anatomy, pressure, and vascular resistance and the LV function.

Management:

See before (management of Univentricular Heart).

Pulmonary Atresia with intact Interventricular septum

Pathophysiology:

- The pulmonary valve is atretic, and the interventricular septum is intact. An interatrial communication (ASD or PFO) and PDA are necessary for survival.
- Pathophysiology is similar to that of tricuspid atresia. The RA hypertrophies and enlarges to shunt systemic venous return to the LA. The LA and LV handle both systemic and pulmonary venous returns and therefore they enlarge. PBF depends on the patency of PDA; closure of PDA after birth results in death.
- The key to management and the ultimate destination in this condition is based on assessment of the **RV size**. It can be divided into three types:
 1. In the *tripartite type*, all three (inlet, trabecular, and infundibular) portions of the RV are present, and the RV is nearly normal in size.
 2. In the *bipartite type*, the inlet and infundibular portions are present (trabecular portion is obliterated).
 3. In the *monopartite type*, only the inlet portion is present. In the monopartite type, the RV is diminutive, and coronary sinusoids are almost always present.
- Confluent pulmonary arteries are usually present with PBF provided through a PDA. TR is commonly present.
- This condition is frequently associated with anomalies of the coronary arteries. The high pressure in the RV is often decompressed through dilated coronary sinusoids into the left or right coronary artery. Such coronary sinusoids occur only in

patients with hypertensive RV but not in patients with tricuspid regurgitation. Often the proximal coronary arteries are obstructed ($\approx 10\%$). If proximal coronary artery obstruction is present, coronary circulation is perfused entirely by desaturated RV blood (RV-dependent coronary circulation). It may cause high surgical mortality.

Natural history:

Without appropriate management (which includes PGE1 infusion and surgery), the prognosis is exceedingly poor. About 50% of these patients die by the end of the first month if not managed properly; about 80% die by 6 months of age. Death usually coincides with the spontaneous closure of the ductus arteriosus.

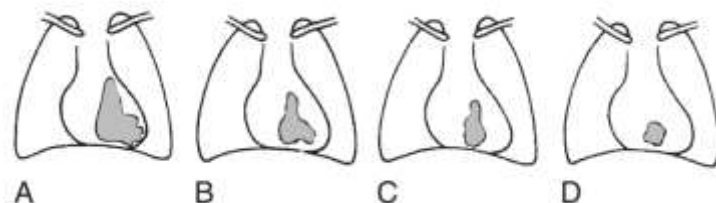


Figure 22-33: Schematic diagram of right ventriculograms that illustrate three types of pulmonary atresia with intact ventricular septum. (A) Normal right ventricle. (B) Tripartite type, which shows all three (inlet, trabecular, and infundibular) portions of the RV. (C) Bipartite type, in which only the inlet and infundibular portions are present. (D) Monopartite type, in which only the inlet portion of the RV is present (almost always associated with coronary sinusoids). Source: Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Clinical Picture:

- **Manifestations:** Severe and progressive cyanosis is present from birth.
- **Auscultation:** S2 is single. Usually no heart murmur is present, but a soft murmur of either TR or a soft continuous murmur of PDA may be audible.
- **ECG:** normal QRS axis (in contrast to the “superior” QRS axis seen in tricuspid atresia), RAH, and LVH (monopartite type) or occasional RVH (tripartite type).

- **Chest radiographs:** The heart size may be normal or large (with RA enlargement). The MPA segment is concave, with markedly decreased PVMs.

Diagnostic Workup:

- **Echocardiography:** Diagnostic features of the condition include: **(A)** a thickened, immobile, atretic pulmonary valve with no Doppler evidence of blood flow through it; **(B)** a hypertrophied RV wall with a small cavity; **(C)** a patent, but small, tricuspid valve; **(D)** a right-to-left atrial shunt through an ASD; and **(E)** ductus arteriosus running vertically from the aortic arch to the PA (i.e., “vertical ductus”).
- **Cardiac catheterization** is recommended for most patients to demonstrate coronary sinusoids (by RV angiogram, demonstrable in 30-50% of cases) and to demonstrate possible coronary artery stenosis or interruption (by an ascending aortogram).

Management:

The aim of treatment is to:

- Secure adequate pulmonary blood flow.
- Decompress the high-pressure RV cavity except in patients with very small RV (unlikely to be of any use) or patients with large coronary fistulae (to avoid sudden coronary steal and ischaemia).
- **Medical:**
 - As soon as the diagnosis is suspected, intravenous PGE1 infusion is started to maintain ductal patency.
 - PDA stenting: In neonates with monopartite RV, who are not likely to be candidates for two-ventricular repair (and are likely to require bidirectional Glenn operation or hemi-Fontan in a few months).
 - A balloon atrial septostomy may be performed to improve the R-to-L atrial shunt, but it is recommended only when a two-ventricular repair is considered not possible (due to the presence of RV sinusoids or too small an RV cavity). The balloon atrial septostomy is not performed in patients with the tripartite type. Such patients may become candidates for RVOT patch, in which an elevated RA pressure is important to maximize RV forward output.

- In patients with membranous atresia, a laser-assisted pulmonary valvotomy with balloon pulmonary valvuloplasty may be a useful alternative to a surgical procedure.
- **Surgical:** Surgical decision making for this condition depends on the RV size and the presence or absence of RV sinusoids or coronary artery anomalies.
- **Tripartite RV:** biventricular repair is usually achieved after initial opening of the outflow tract (either with balloon or surgery).
- **A very small RV:** These patients will progress down a Fontan pathway (stabilized with a BT shunt or ductal stent, then a bidirectional Glenn shunt then Fontan operation).
- **Borderline cases** (where the RV is felt to be too small to support the circulation unaided): can undergo a bidirectional Glenn shunt with either closing the atrial septum or leaving a small ASD. This is known as the 'One and half ventricle repair', where the RV is essentially handling only the IVC return.

Hypoplastic Left Heart Syndrome (HLHS)

Pathophysiology:

- HLHS includes a group of anomalies characterized by hypoplasia of the LV (in association with atresia or severe stenosis of the aortic and/or mitral valves) and hypoplasia of the ascending aorta and the aortic arch. The LV is small or totally atretic. The atrial septum is intact with a normal PFO. A VSD occurs in about 10% of the patients. CoA frequently is an associated finding (up to 75%).
- During fetal life, the PVR is higher than the SVR and the dominant RV maintains normal perfusion pressure in the descending aorta through the ductal R-L shunt, even in the presence of the nonfunctioning hypoplastic LV.
- After birth, difficulties arise for two reasons: **(1)** reduction of PVR (with the onset of respiration) and **(2)** closure of the ductus arteriosus. This results in a marked reduction in the aortic perfusing pressure and systemic hypoperfusion, producing circulatory shock and metabolic acidosis.
- Also, the increased PBF in the presence of the nonfunctioning LV results in an elevated LA pressure and pulmonary edema.

- A high prevalence (up to 29%) of brain abnormalities has been reported, including agenesis of the corpus callosum, holoprosencephaly, microencephaly, and immature cortical mantle.

Natural history:

Pulmonary edema and CHF develop in the first week of life. Circulatory shock and progressive hypoxemia and acidosis result in death, usually in the first month of life.

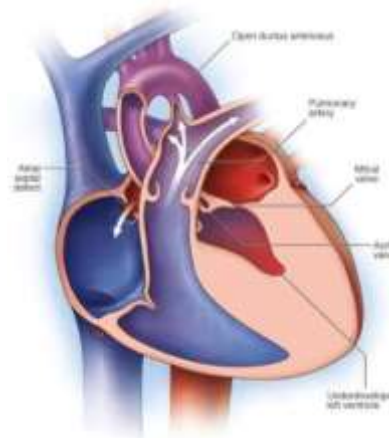


Figure 22-34: Hypoplastic Left Heart Syndrome illustration.

Clinical Picture:

- **Manifestations:** The neonate is critically ill in the first few hours of life, with tachycardia, tachypnea, and pulmonary crackles. The patient may not have severe cyanosis but grayish blue color with poor perfusion. Poor peripheral pulses and vasoconstricted extremities are characteristic.
- **Auscultation:** S2 is loud and single. Heart murmur is usually absent.
- **ECG:** RVH (because V₅ and V₆ electrodes are placed over the dilated RV).

- **Chest radiographs:** pulmonary venous congestion or pulmonary edema. The heart is only mildly enlarged.

Diagnostic Workup:

- **Echocardiography** is diagnostic. The LV cavity is diminutive. The RV cavity is markedly dilated, and the tricuspid valve is large. Severe hypoplasia of the aorta and aortic annulus and the absent or distorted mitral valve are usually imaged. A partially constricted PDA may be imaged.
- A neurologic evaluation, including imaging of the head, should be obtained because of a high prevalence of neurodevelopmental abnormalities seen in this condition. MRI of the head appears to be more sensitive than the head ultrasound scan and the latter shows frequent false positive results.

Management

- **Medical:**

- The patient should be intubated and ventilated, and metabolic acidosis should be corrected.
- An intravenous infusion of PGE1 may produce temporary improvement.
- Balloon atrial septostomy may help decompress the LA and temporarily improve oxygenation.
- **Surgical:** Three options are available in the management of these infants: **(1)** the Norwood operation (followed by a Fontan-type operation), **(2)** a hybrid operation (followed by a Fontan-type operation), and **(3)** cardiac transplantation.

N.B: Norwood procedure has three components: **(1)** The first stage, performed in the first few days of life, comprises a reconstruction of the systemic outflow tract from the heart by connecting the pulmonary artery to the aorta. Blood flow to the lungs is achieved by a MBT shunt or RV-to-PA conduit. At the same procedure, an open atrial septectomy is performed so that there is no restriction of blood flow from the pulmonary veins into the RV. **(2)** The Norwood II procedure is performed at about 4-6 months of age. At that time, the BT shunt or RV-to-PA conduit is removed, and the pulmonary circulation is restored by connecting the SVC to the PA. **(3)** The final stage, the Fontan procedure, is performed at about 4-6 years of age.

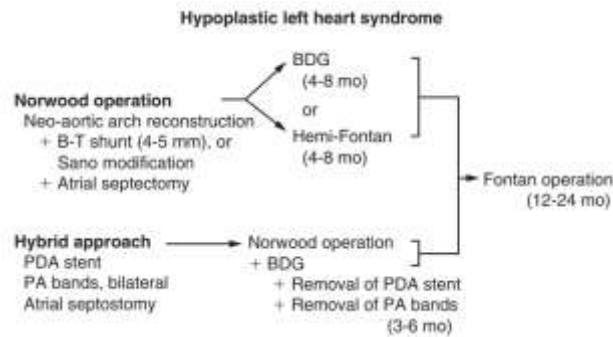


Figure 22-35: Surgical approaches to hypoplastic left heart syndrome. BDG, bidirectional Glenn; B-T, Blalock-Taussig. **Source:** Park MK: Park's Pediatric Cardiology for Practitioners, ed 6, Philadelphia, Mosby, 2014.

Fontan operation

The Fontan procedure is a palliative surgery that redirects the systemic venous return directly to the pulmonary artery without passing through the RV (= atriopulmonary connection). It was introduced in 1968 and has become the definitive treatment for suitable patients who have a “functionally single ventricle”.

This procedure relieves the chronic volume load on the systemic ventricle that is pumping to both the pulmonary and systemic circulations. What is interesting is that blood flows passively to the PA without an interposed RV, as long as the PA pressure is not increased. In a way, humans who have a normal PA pressure may live without RV for many years; the RV may be forgone for a passive conduit in patients with normal PA pressure.

The venous pressure must be high enough, higher than the pulmonary pressure, to let blood flow towards the pulmonary artery. The systemic venous pressure is, therefore, elevated chronically and allows forward flow. The RA is chronically and severely enlarged. The procedure cannot be performed in patients with pulmonary hypertension.

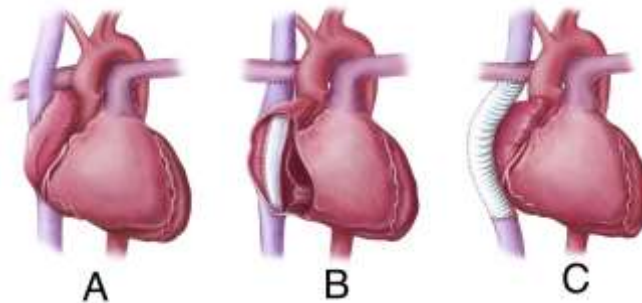


Figure 22-36: A set of illustrations showing the historical changes in the Fontan procedure. (A) Classic Fontan procedure. (B) Lateral tunnel procedure. (C) Extra-cardiac Fontan procedure. Source: Sathananthan, G., Lowe, B. S., & Hornung, T. S. (2016). The Fontan Circulation. *European Medical Journal Cardiology*, 4(1), 76-83.

Table 22-23: Fontan Pathway:

- **Stage I: One of the following procedures is done in preparation for a future Fontan operation.**

1. Blalock-Taussig shunt, when PBF is small
2. PA banding, when PBF is excessive
3. Damus-Kaye-Stansel + shunt operation (for Tricuspid Atresia + TGA + restrictive VSD)

Medical follow-up after stage I. Watch for:

- A. Cyanosis (O_2 sat. < 75%): cardiac catheterization or MRI to find the cause.
- B. Poor weight gain (CHF from too much PBF): tightening of PA band may be necessary.

- **Stage II (at 3 to 6 mo): Bidirectional Glenn (BDG) or hemi-Fontan operation**

Medical follow-up after stage II. Watch for the following:

- A. A gradual decrease in O_2 saturation (< 75%) may be caused by:
 - (1) Opening of venous collaterals
 - (2) Pulmonary AV fistula (due to the absence of hepatic inhibitory factor)
 - Perform cardiac catheterization (to find and occlude venous collaterals) or

- Proceed with Fontan operation
- B. Transient hypertension 1-2 wk postoperatively: may use ACE inhibitors.
- C. Cardiac catheterization by 12 mo. after stage II to assess risk factors.
- **Stage III (Fontan operation)** within 1-2 yrs after stage II operation.
 1. “Lateral tunnel” Fontan (with 4 mm fenestration); device closure of the fenestration 1-2 yr later, or
 2. An extracardiac conduit (usually without fenestration)

Exam and long-term complications:

Fontan patients have a quiet auscultation without any significant murmur; a murmur suggests associated abnormalities. They survive until early adulthood (20s) before they develop failure of their single ventricle and arrhythmias.

Complications of the Fontan-Operation:

- **Early Complications:** may include the following:
 - Low cardiac output, heart failure, or both are early postoperative complications.
 - Persistent pleural effusion: It may be the result of a sudden rise in the systemic venous or RA pressure. It occurs more often on the right side. The presence of aortopulmonary collaterals increases the risk of prolonged pleural effusion. Coil occlusion of these vessels before surgery can ameliorate this problem.
 - Thrombus formation in the systemic venous pathways may result from a sluggish blood flow. The risk is highest in the first several weeks to months after the operation, although the risk is present for the lifetime.
 - Although rare, acute liver dysfunction with alanine transaminase greater than 1000 U/L can occur during the first week after surgery, possibly resulting from hepatic hypoperfusion (caused by low cardiac output).
- **Late Complications:**
 - Liver dysfunction, liver cirrhosis, and hepatocellular carcinoma, so regular liver imaging and laboratory assessment should be performed.

- Supraventricular arrhythmia: Early-onset arrhythmias occur in 15% of patients. The incidence of late-onset SVT continues to increase (6% at 1 year, 12% at 3 years, and 17% at 5 years). Extra-cardiac conduit (instead of intra-atrial lateral tunnel) may help reduce incidence of late arrhythmias.
- A progressive decrease in arterial oxygen saturation may result from obstruction of the venous pathways, leakage in the intraatrial baffle, or development of pulmonary AV fistula.
- Protein-losing enteropathy, from the chronically elevated venous pressure. Increased PVR, decreased cardiac index, and increased ventricular end-diastolic pressure were coincidental findings with the condition. The incidence of protein-losing enteropathy among survivors is 10% and carries a poor prognosis (50% mortality at 5 years). Heart transplantation should be considered for these patients.
- Thromboembolism can occur in up to 10% of the patients after Fontan operation.

Diagnostic work-up:

- **Echocardiography** is the first-line diagnostic tool, providing information on ventricular and valve function. To image the Fontan pathway, TOE or other imaging modalities are generally required.
- **Annual blood tests** should include haematology, serum albumin, and liver and renal function. When protein losing enteropathy is suspected, a1-antitrypsin clearance must be calculated.
- **CMR** is helpful for evaluation of the Fontan pathway, collaterals, and pulmonary veins (e.g. right pulmonary vein obstruction by enlarged RA) and for thrombus, all of which CCT can also provide. CCT requires experience to mitigate streaming artefact and false positive diagnosis of thrombus. CMR is regularly performed for ventricular volumes, Fontan pathway patency and flows, to evaluate AV valve regurgitation, subaortic obstruction, myocardial fibrosis, and for detection of thrombus.
- **Cardiac catheterization** should be performed at a low threshold in cases of unexplained oedema, exercise deterioration, new-onset arrhythmia, cyanosis, and haemoptysis. It provides information on ventricular and valvular function, haemodynamics (e.g., PVR and Fontan obstruction) and anomalous vascular connections.

Medical treatment:

- **Anticoagulation:** right atrial blood stasis and disturbed coagulation may predispose to thrombosis. The potential for subclinical, recurrent pulmonary embolism (eventually leading to a rise in PVR) and systemic embolism have led to a recommendation, by some, for lifelong anticoagulation. There is, however, no evidence of benefit, and practice varies between centres. Anticoagulation is indicated in the presence, or with a history, of atrial thrombus, atrial arrhythmias, or thromboembolic events.
- **Antiarrhythmic therapy:** loss of sinus rhythm may precipitate rapid haemodynamic decline and atrial arrhythmias. Sustained atrial arrhythmia with rapid AV conduction is a medical emergency.
 - Electrical cardioversion is the mainstay of treatment, as drug therapy is often ineffective.
 - Amiodarone may be effective in preventing recurrence, but it has many long-term side effects. Sotalol can be an alternative.
 - There should be a low threshold for radiofrequency ablation, although these are difficult arrhythmias to treat in the catheterization laboratory.
 - Antitachycardia atrial PMs may assist. If AV pacing is required, this will need an epicardial approach.
 - Occurrence of arrhythmias should prompt haemodynamic evaluation. In addition, a proactive approach of EP evaluation and ablation therapy (where appropriate) should be considered, including Fontan conversion with concomitant arrhythmia surgery. ICD therapy may be considered in selected patients.
- **Therapy of protein losing enteropathy:** medical therapy remains challenging and various treatments have been proposed (after exclusion of haemodynamic problems) including salt restriction, high protein diet, diuretics, ACEIs (may be poorly tolerated), steroids, albumin infusion, chronic subcutaneous heparin, creation of a fenestration (by interventional catheter), and eventually, consideration of transplantation.
- **Pulmonary vasodilators:** ERAs and PDE-5 inhibitors may be considered in selected patients with elevated pulmonary pressure/resistance in the absence of elevated ventricular end diastolic pressure. Data on the routine use of these medications in Fontan patients are limited at present.

Table 22-24: ESC recommendations for Special considerations and recommendations for intervention after Fontan operation:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Sustained atrial arrhythmia with rapid AV conduction is a medical emergency and should be promptly treated with electrical cardioversion.</i> | I | C |
| <i>Anticoagulation is indicated in the presence, or with a history, of atrial thrombus, atrial arrhythmias, or thromboembolic events.</i> | I | C |
| <i>It is recommended that women with a Fontan circulation and any complication are counselled against pregnancy.</i> | I | C |
| <i>Cardiac catheterization is recommended at a low threshold in cases of unexplained oedema, exercise deterioration, new-onset arrhythmia, cyanosis, and hemoptysis.</i> | I | C |
| <i>In patients with arrhythmias, a proactive approach of electrophysiologic evaluation and ablation (where appropriate) should be considered.</i> | IIa | C |
| <i>Regular liver imaging (ultrasound, CT, MRI) should be considered.</i> | IIa | C |
| <i>Endothelin receptor antagonists and phosphodiesterase-5 inhibitors may be considered in selected patients with elevated pulmonary pressure/resistance in the absence of elevated ventricular end diastolic pressure.</i> | IIb | C |
| <i>In selected patients with significant cyanosis, device closure of a fenestration may be considered but requires careful evaluation before intervention to exclude induction of systemic venous pressure increase or fall in cardiac output.</i> | IIb | C |

Follow-up recommendations:

As a result of these many complex issues, the care of Fontan patients is one of the major challenges.

- All Fontan patients should be followed in specialized ACHD centres, usually at least annually, with echocardiography, ECG, blood tests, and exercise testing.
- For adults, it appears reasonable to perform a baseline hepatic assessment with MRI at the first visit to guide the frequency and mode of follow-up based on the degree of pre-existing hepatic changes.
In addition, yearly follow-up hepatic assessments including, for example, liver ultrasound and alpha-fetoprotein measurement, should be considered after consultation with local hepatology services.
- Comprehensive assessment is mandatory for patients with manifestations of the 'failing Fontan' complex, with particular care to exclude even minor obstructions to cavopulmonary flow and pulmonary venous return, which may have a major hemodynamic impact.

Coronary anomalies

Embryologic development of the coronary artery is not completely understood, although altered coronary embryogenesis may result in: **(1)** abnormal coronary origins from the aorta (AAOCA) or **(2)** abnormal coronary origins from pulmonary artery (ACAPA) or **(3)** incomplete development (leading to coronary fistulae or sinusoids).

Anomalous aortic origin of a coronary artery

This anomaly can involve either the right coronary originating from the left sinus of Valsalva (more common) or the left coronary originating from the right sinus of Valsalva, and rarely more posteriorly from the non-coronary sinus.

Pathophysiology:

Several pathophysiologic mechanisms have been postulated for the occurrence of SCD in those patients. These include occlusion and/or compression of the anomalous coronary artery (intramural segment, interarterial course) and ostial abnormalities (slit-like and stenotic ostium), particularly during exercise, leading to myocardial ischemia and development of ventricular arrhythmia.

Risk stratification:

Risk assessment for SCD is difficult (due to lack of data). However, proposed risk factors may include:

- Age < 35 years: Autopsy series show that most patients are < 35 years and die during or after exercise.
- Myocardial fibrosis has been demonstrated, suggesting myocardial ischaemia may play a role.
- Left coronary artery arising from the right sinus is more malignant than the RCA from the left sinus.
- High risk anatomical features: High orifice > 1 cm above the sinotubular junction, ostial stenosis, slit-like/fish-mouth shaped orifice, acute-angle take-off, intramural course and its length, or interarterial course and hypoplasia of the proximal segment.
- Level of exercise (e.g., competitive sports).

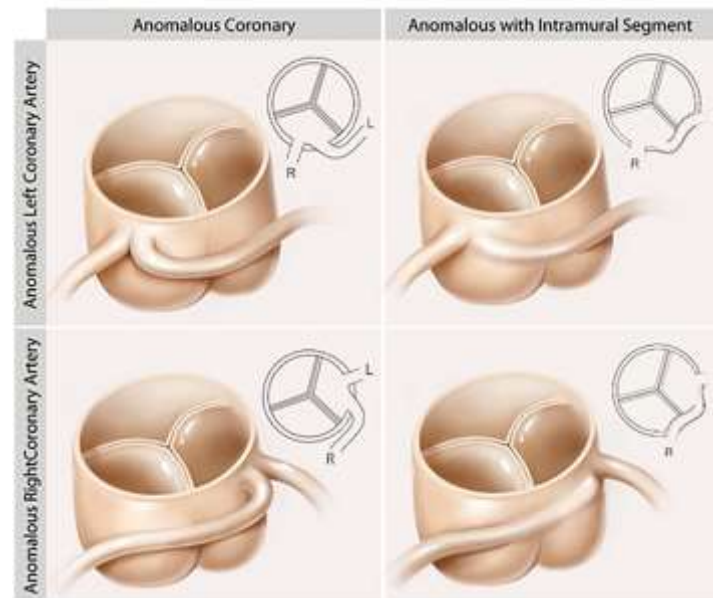


Figure 22-37: Anomalous coronary arteries arising from the aorta. Source: Texas Children's Hospital.

Diagnostic work-up:

- **Presentation:** Chest pain, exertional syncope and SCD may be the first manifestation of AOCA.
- CCT is the preferred technique for the evaluation of high-risk anatomy, including features such as an intramural, interarterial course and orifice anomalies.
- Assessment of physical stress-induced ischemia is the key to decision making. Exercise stress test (EST) is recommended. However, it has a low sensitivity to detect inducible ischemia (SCD during exertion has been reported in patients with coronary artery anomalies who had a normal EST before the event).

Management:

| Table 22-25: ESC Recommendations for the management of patients with anomalous coronary arteries: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Non-pharmacological functional imaging (e.g., nuclear study, echocardiography, or CMR with physical stress) is recommended in patients with coronary anomalies to confirm/exclude myocardial ischemia. | I | C |
| Surgery is recommended for AAOCA in patients with typical angina symptoms who present with evidence of stress-induced myocardial ischemia in a matching territory <u>or</u> high-risk anatomy. | I | C |
| Surgery should be considered in asymptomatic patients with: <ul style="list-style-type: none"> - AAOCA (right or left) and evidence of myocardial ischemia. - AAOLCA and no evidence of myocardial ischemia but a high-risk anatomy. | IIa | C |
| Surgery may be considered for: <ul style="list-style-type: none"> - symptomatic patients with AAOCA even if there is no evidence of myocardial ischemia or high-risk anatomy. - asymptomatic patients with AAOLCA without myocardial ischemia and without high-risk anatomy when they present at young age (< 35 years) | IIb | C |
| Surgery is not recommended for AAORCA in asymptomatic patients without myocardial ischemia and without high-risk anatomy. | III | C |

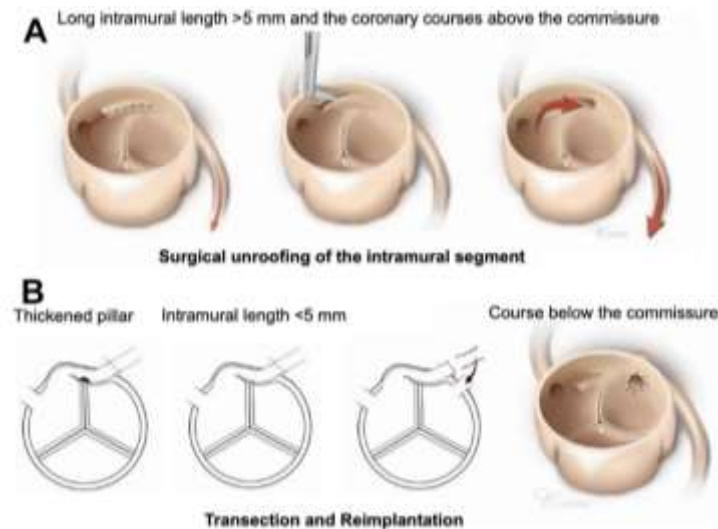


Figure 22-38: Diagrams of surgical unroofing of an intramural course (A) versus transection and reimplantation (B) based on anatomic features on CTA and surgical inspection. Source: Texas Children's Hospital.

Anomalous coronary artery from the pulmonary artery

Anomalous origin of the left coronary artery from pulmonary artery (ALCAPA) is a rare disease, occurring in 1 in 3,00,000 live births, that if untreated causes heart failure, myocardial ischemia, and death. The incidence of ALCAPA is thought to be higher than that of anomalous origin of the right coronary artery from pulmonary artery (ARCAPA) due to the proximity of the left coronary bud to the pulmonary artery sinus.

Pathophysiology:

Fetuses with ALCAPA remain asymptomatic because the diastolic pressure in the pulmonary artery and aorta are similar during fetal circulation.

After birth, when the PVR starts to drop, symptoms start to appear in most infants due to a reversal flow through left coronary artery. This leads to coronary artery steal and further progression of myocardial ischemia. This may be exacerbated during periods of stress, which in infants can occur during feedings.

The surrounding arteries start to create collateral blood flow to the affected ventricle.

Diagnosis:

○ **Presentation:**

- **ALCAPA:** can present as a silent or symptomatic myocardial infarction, LV dysfunction, VTs, or even SCD. Patients may also present with volume overload due to L-R shunt causing HF symptoms.
- **ARCAPA:** ARCAPA has frequently been diagnosed incidentally. Due to reduced RV workload and oxygen demands compared with that of the LV, ventricular ischemia is less prominent in ARCAPA than ALCAPA. However, ARCAPA patients with a right dominant coronary circulation do exhibit chronic ischemia than left dominant circulation.
- **Echocardiography:** This condition is usually suspected on echocardiography either by direct visualization of the coronary artery from the pulmonary artery or by secondary signs of ventricular dysfunction, mitral regurgitation, echogenic papillary muscles, dilation of RCA (due to collateral formation in ALCAPA) as well as the presence of flow signals within the myocardium suggesting collateral flow.
- **CTA or CMR** may assist in more definitive diagnosis and provide additional information.

Management:

- Dual coronary system repair, including coronary button transfer with or without an interposition graft, is preferred.
- CABG with closure of the ACAPA should be reserved for those in whom coronary transfer is not feasible.

Table 22-26: ESC Recommendations for the management of patients with anomalous coronary arteries:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Surgery is recommended in patients with ALCAPA.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Surgery is recommended in patients with ARCAPA and symptoms attributable to anomalous coronary artery.</i> | I | C |
| <i>Surgery should be considered for ARCAPA in asymptomatic patients with ventricular dysfunction, or myocardial ischemia attributable to coronary anomaly.</i> | Ila | C |

Coronary artery fistula (CAF)

- Coronary artery fistula (CAF) is an abnormal connection between a coronary artery and an adjacent vein, cardiac chamber, or other mediastinal structures.
- It is usually diagnosed incidentally during coronary angiography or noninvasive cardiac imaging.
- The majority of CAFs are congenital, but may be iatrogenic.
- Clinical sequelae include cardiac chamber dilatation and dyspnea, as well as symptoms of ischemia.
- Although most patients have a single CAF, 20% of patients have fistulas originating from 2 or more coronary arteries.
- CAFs can be classified as small, medium, or large if the fistula diameter is < 1, 1-2, or > 2 times the largest diameter of the coronary vessel not feeding the coronary fistula, respectively.
- Small CAFs likely close spontaneously, while larger CAFs require surgical or transcatheter closure.

Management:

- **Indications for CAF Closure:** Symptomatic medium or large CAF with:
 - Evidence of ischemia in the feeder artery territory.
 - Arrhythmia thought to be related to CAF.
 - Endarteritis.
 - Vessel rupture.
 - Cardiac chamber enlargement.

- Ventricular dysfunction.
- **Technique of Closure:**
 - **Surgical closure** if coronary artery fistula from distal coronary bed with enlarged proximal coronary artery ≥ 10 mm or if significant myocardium is at risk ⁽¹⁾.
 - **Transcatherter closure** if coronary artery fistula from proximal coronary bed or from distal coronary bed with no significant enlargement of proximal coronary artery (< 10 mm).
- **Procedural Complications:**
 - As in all coronary procedures, the risk for vessel trauma or dissection, rupture, and coronary pseudostenosis during wire and catheter delivery exists.
 - For larger fistulas, there is a risk for device embolization.
 - Equipment thrombosis. Full i.v heparin administration with goal activated clotting time of 250 to 300 ms is recommended to reduce the risk. Partial reversal with protamine is given at the end of the case to enhance clotting of the released device before final angiography.

References and suggested readings:

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- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).

(1) Significant myocardium at risk is defined by the number and sizes of branches that might be compromised with closure of coronary artery fistula.

- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
- Dudek, R. (2014). *Brs Embryology* (6th edition). Lippincott Williams And Wilkin.

Table 22-27: Common Surgical Procedures for Congenital heart diseases:

| Procedure | Description | Intent | Result |
|-------------------------------|--|------------|---|
| Blalock-Taussig | Subclavian artery to PA anastomosis | Palliative | Increase PBF |
| Central shunt | Anastomosis between PA and aorta | Palliative | Increase PBF |
| Fontan | Anastomosis between RA and PA | Palliative | Increase PBF in univentricular heart. |
| Hemi-Fontan | SVC to PA anastomosis with baffle placed in the right atrium, so that IVC blood flow goes across ASD to left heart | Palliative | Increase PBF and sets the stage for Fontan. |
| Glenn | SVC to RA anastomosis | Palliative | Increase PBF |
| Jatene Arterial switch | Transaction of the aorta and PA with reimplantation onto the proper ventricles, coronary arteries reimplanted. | Corrective | Creates normal relationship between the ventricles and great vessels in d-TGA |
| Konno | Replacement of aortic valve with aortic valve annular enlargement | Corrective | Alleviates subaortic obstruction and replaces abnormal aortic valve. |
| Mustard/Senning | Atrial switch with intra-atrial baffle made of pericardium (Mustard) or atrial wall edge (senning) | Corrective | Reestablish proper flow sequence to PA and aorta in d-TGA. |
| Norwood | PA anastomosis to aorta | Palliative | Increase flow to aorta for subaortic obstruction with single ventricle |
| PA band | Constrictive band around main PA | Palliative | Decrease BPF |
| Potts | Descending aorta to P shunt | Palliative | Increase PBF (rarely done anymore) |

| | | | |
|------------------|--|------------|---|
| Rashkind | Atrial septostomy with catheter balloon | Palliative | Increase mixing of blood |
| Rastelli | Closure of VSD + valve conduit from. RV to PA | Corrective | Increase PBF, may reestablish proper sequence of flow to aorta and PA |
| Ross | Pulmonary autograft to aorta + Pulmonary homograft | Corrective | Correction of aortic stenosis |
| Waterston | Ascending aorta to RPA anastomosis | Palliative | Increase PBF (rarely done anymore) |

Section

VII

Pulmonary Circulation Disorders

TO THE POINT

Chapter 23:

Pulmonary Embolism

Epidemiology:

Venous thromboembolism (VTE), clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke. In epidemiological studies, annual incidence rates for PE range from 39115 per 100 000 population; for DVT, incidence rates range from 53162 per 100 000 population. The incidence of VTE is almost eight times higher in individuals aged ≥ 80 years than in the fifth decade of life. Time trend analyses suggest that case fatality rates of acute PE may be decreasing. Increased use of more effective therapies and interventions, and possibly better adherence to guidelines, has most likely exerted a significant positive effect on the prognosis of PE in recent years.

Predisposing factors:

VTE is considered to be a consequence of the interaction between patient-related (usually permanent) risk factors and setting-related (usually temporary) risk factors.

Table 23-1: Predisposing factors for venous thromboembolism:

Strong risk factors (odds ratio "OR" > 10)

- *Fracture of lower limb*
- *Hip or knee replacement*
- *Major trauma*
- *Hospitalization for HF or AF/flutter (within previous 3 months)*
- *Myocardial infarction (within previous 3 months)*

- *Previous VTE*
- *Spinal cord injury*

Moderate risk factors (OR 2-9)

- *Arthroscopic knee surgery*
- *Autoimmune diseases*
- *Blood transfusion*
- *Central venous lines*
- *Intravenous catheters and leads*
- *Chemotherapy*
- *Congestive heart failure or respiratory failure*
- *Erythropoiesis-stimulating agents*
- *Hormone replacement therapy (depends on formulation)*
- *In vitro fertilization*
- *Oral contraceptive therapy*
- *Post-partum period*
- *Infection (specifically pneumonia, urinary tract infection, and HIV)*
- *Inflammatory bowel disease*
- *Cancer (highest risk in metastatic disease)*
- *Paralytic stroke*
- *Superficial vein thrombosis*
- *Thrombophilia*

Weak risk factors (OR < 2)

- *Bed rest > 3 days*
- *Diabetes mellitus*

- *Arterial hypertension*
- *Immobility due to sitting (e.g. prolonged car or air travel)*
- *Increasing age*
- *Laparoscopic surgery (e.g. cholecystectomy)*
- *Obesity*
- *Pregnancy*
- *Varicose veins*

Pathophysiology:

Acute PE interferes with both circulation and gas exchange. Right ventricular (RV) failure due to acute pressure overload is considered the primary cause of death in severe PE.

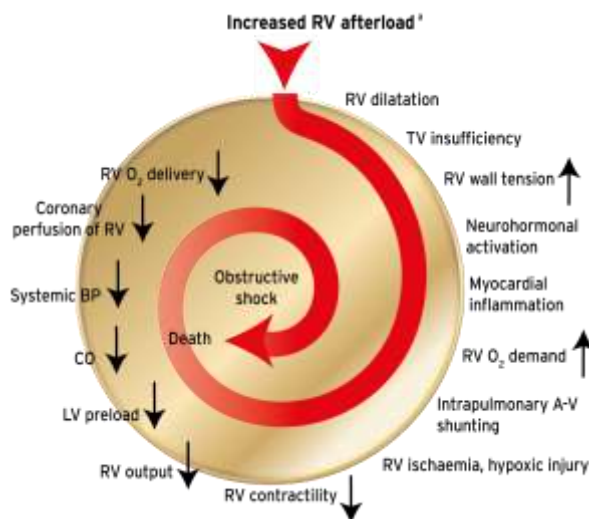


Figure 23-1: Key factors contributing to haemodynamic collapse and death in acute pulmonary embolism. A) The exact sequence of events following the increase in RV afterload is not fully understood. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism modified from Konstantinides et al.

Hemodynamic instability, indicate a high risk of early (in-hospital or 30 day) mortality. High-risk PE is defined by hemodynamic instability and encompasses one of the following clinical presentation:

1. Cardiac arrest, or
2. Obstructive shock (systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or
3. Persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop ≥ 40 mmHg for > 15 min, not caused by new-onset arrhythmia, hypovolemia, or sepsis).

Diagnosis:

▪ Clinical presentation:

The clinical signs and symptoms of acute PE are non-specific. In most cases, PE is suspected in a patient with dyspnea, chest pain, presyncope or syncope, or hemoptysis. In some cases, PE may be asymptomatic or discovered incidentally during diagnostic workup for another disease.

In addition to symptoms, knowledge of the predisposing factors for VTE is important in determining the clinical probability of the disease, which increases with the number of predisposing factors present; however, in 40% of patients with PE, no predisposing factors are found. Hypoxemia is frequent, but $\leq 40\%$ of patients have normal arterial oxygen saturation (SaO₂) and 20% have a normal alveolar-arterial oxygen gradient. Hypocapnia is also often present.

▪ **Assessment of clinical (pre-test) probability:**

The combination of symptoms and clinical findings with the presence of predisposing factors for VTE allows the classification of patients with suspected PE into distinct categories of clinical or pre-test probability, which correspond to an increasing actual prevalence of confirmed PE. This pre-test assessment can be done either by implicit (empirical) clinical judgement or by using prediction rules.

As the post-test (i.e. after an imaging test) probability of PE depends not only on the characteristics of the diagnostic test itself but also on the pretest probability, this is a key step in all diagnostic algorithms for PE.

Regardless of the score used, the proportion of patients with confirmed PE can be expected to be 10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high probability category. When the two-level classification is used, the proportion of patients with confirmed PE is 12% in the PE-unlikely category and 30% in the PE-likely category.

| Table 23-2: The revised Geneva clinical prediction rule for pulmonary embolism: | | |
|---|-------------------------------|--------------------|
| Items | Clinical decision rule points | |
| | Original version | Simplified version |
| <i>Previous PE or DVT</i> | 3 | 1 |
| <i>Heart rate</i> | | |

| | | |
|---|-------------|------------|
| <i>75-94 b.p.m.</i> | 3 | 1 |
| <i>≥ 95 b.p.m.</i> | 5 | 2 |
| <i>Surgery or fracture within the past month</i> | 2 | 1 |
| <i>Hemoptysis</i> | 2 | 1 |
| <i>Active cancer</i> | 2 | 1 |
| <i>Unilateral lower-limb pain</i> | 3 | 1 |
| <i>Pain on lower-limb deep venous palpation and unilateral oedema</i> | 4 | 1 |
| <i>Age > 65 years</i> | 1 | 1 |
| Clinical probability | | |
| Three-level score | | |
| <i>Low</i> | 0-3 | 0-1 |
| <i>Intermediate</i> | 4-10 | 2-4 |
| <i>High</i> | ≥ 11 | ≥ 5 |
| Two-level score | | |
| <i>PE-unlikely</i> | 0-5 | 0-2 |
| <i>PE-likely</i> | ≥ 6 | ≥ 3 |

Table 23-3: The Wells clinical prediction rule for pulmonary embolism

| Items | Clinical decision rule points | |
|----------------------------------|-------------------------------|--------------------|
| | Original version | Simplified version |
| <i>Previous PE or DVT</i> | 1.5 | 1 |
| <i>Heart rate >100 b.p.m.</i> | 1.5 | 1 |

| | | |
|--|-----|-----|
| <i>Surgery or immobilization within 4 weeks</i> | 1.5 | 1 |
| <i>Hemoptysis</i> | 1 | 1 |
| <i>Active cancer</i> | 1 | 1 |
| <i>Clinical signs of DVT</i> | 3 | 1 |
| <i>Alternative diagnosis less likely than PE</i> | 3 | 1 |
| Clinical probability | | |
| Three-level score | | |
| <i>Low</i> | 0-1 | N/A |
| <i>Intermediate</i> | 2-6 | N/A |
| <i>High</i> | ≥ 7 | N/A |
| Two-level score | | |
| <i>PE unlikely</i> | < 4 | < 1 |
| <i>PE likely</i> | ≥ 5 | ≥ 2 |

- **D-dimer testing:** D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE.

The specificity of D-dimer in suspected PE decreases steadily with age to 10% in patients > 80 years of age. Using age-adjusted cut-off (age x 10 mg/L, for patients aged > 50 years) may improve the performance of D-dimer testing in the elderly.

- **Imaging tests:**
- **Multidetector CTPA** is the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to the subsegmental level.

- The planar ventilation/perfusion **[V/Q (lung scintigraphy)] scan** may preferentially be applied in outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnant women, in patients with history of contrast medium-induced anaphylaxis, and patients with severe renal failure.
- **Single-photon emission CT (SPECT) imaging**, with or without low-dose CT, may decrease the proportion of non-diagnostic scans.
- **Pulmonary angiography** is now rarely performed as less-invasive CTPA offers similar diagnostic accuracy.
- **Magnetic resonance angiography (MRA)** is not yet ready for clinical practice due to its low sensitivity, the high proportion of inconclusive MRA scans, and its low availability in most emergency settings.
- **Compression ultrasonography**: CUS shows a DVT in 30-50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing. However, patients in whom PE is indirectly confirmed by the presence of a proximal DVT should undergo risk assessment for PE severity and the risk of early death.

Table 23-4: Imaging tests for diagnosis of pulmonary embolism:

| Strengths | | Weaknesses/limitations | Radiation issues ⁽¹⁾ |
|-------------|---|---|--|
| CTPA | <ul style="list-style-type: none"> - Readily available around the clock in most centres - Excellent accuracy - Strong validation in prospective management outcome studies - Low rate of inconclusive results (35%) | <ul style="list-style-type: none"> • Radiation exposure • Exposure to iodine contrast: <ul style="list-style-type: none"> - limited use in iodine allergy and hyperthyroidism - risks in pregnant and breast-feeding women | <ul style="list-style-type: none"> - Radiation effective dose 3-10 mSv ⁽²⁾ - Significant radiation exposure to young female breast tissue |

(1) In this section, effective radiation dose is expressed in mSv [dose in mSv = absorbed dose in mGy radiation weighting factor (1.0 for X rays) tissue weighting factor]. This reflects the effective doses of all organs that have been exposed, that is, the overall radiation dose to the body from the imaging test.

(2) For comparison, the whole-body effective dose of a chest X-ray examination is 0.1 mSv.

| | | | |
|------------------------------|--|---|---|
| | <ul style="list-style-type: none"> - May provide alternative diagnosis if PE excluded - Short acquisition time | <ul style="list-style-type: none"> - contraindicated in severe renal failure • Tendency to overuse because of easy accessibility • Clinical relevance of CTPA diagnosis of subsegmental PE unknown | |
| Planar V/Q scan | <ul style="list-style-type: none"> - Almost no contraindications - Relatively inexpensive - Strong validation in prospective management outcome studies | <ul style="list-style-type: none"> - Not readily available in all centres - Interobserver variability in interpretation - Results reported as likelihood ratios - Inconclusive in 50% of cases - Cannot provide alternative diagnosis if PE excluded | Lower radiation than CTPA, effective dose 2 mSv |
| V/Q SPECT | <ul style="list-style-type: none"> - Almost no contraindications - Lowest rate of non diagnostic tests (<3%) - High accuracy according to available data - Binary interpretation ('PE' vs. 'no PE') | <ul style="list-style-type: none"> - Variability of techniques - Variability of diagnostic criteria - Cannot provide alternative diagnosis if PE excluded - No validation in prospective management outcome studies | Lower radiation than CTPA, effective dose 2 mSv |
| Pulmonary angiography | <ul style="list-style-type: none"> - Historical gold standard | <ul style="list-style-type: none"> - Invasive procedure - Not readily available in all centres | Highest radiation, effective dose 10-20 mSv |

- **Echocardiography**

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function.

Echocardiographic examination is not mandatory as part of the routine diagnostic workup in hemodynamically stable patients with suspected PE, although it may be useful in the differential diagnosis of acute dyspnoea. This is in contrast to suspected high-risk PE, in which the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of hemodynamic instability.

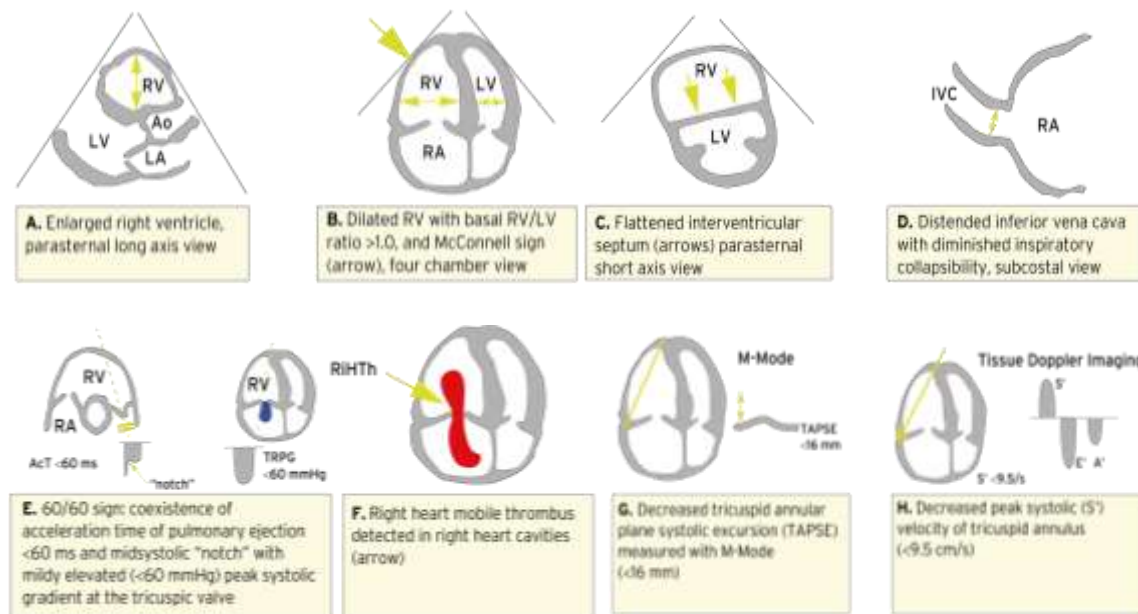


Figure 23-2: Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload. A0 = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = RVOT Doppler acceleration time; Ao = aorta; RiHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.
Source: 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

Table 23-5: ESC Recommendations for diagnosis of PE:

| Recommendations | Class | Level |
|---|-------|-------|
| Suspected PE with hemodynamic instability: | | |
| <i>In suspected high-risk PE, as indicated by the presence of haemodynamic instability, bedside echocardiography or emergency CTPA (depending on availability and clinical circumstances) is recommended for diagnosis.</i> | I | C |

| | | |
|---|------------|----------|
| <i>It is recommended that i.v. anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with suspected high-risk PE.</i> | I | C |
| Suspected PE without hemodynamic instability: | | |
| <i>The use of validated criteria for diagnosing PE is recommended.</i> | I | B |
| <i>Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic workup is in progress.</i> | I | C |
| Clinical evaluation: | | |
| <i>It is recommended that the diagnostic strategy be based on clinical probability, assessed either by clinical judgement or by a validated prediction rule.</i> | I | A |
| D-dimer: | | |
| <i>Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are PE-unlikely, to reduce the need for unnecessary imaging and irradiation.</i> | I | A |
| <i>As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age adjusted cut-off (age x 10 mg/L, in patients aged >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or those that are PE-unlikely.</i> | IIa | B |
| <i>As an alternative to the fixed or age-adjusted D-dimer cut-off, D-dimer levels adapted to clinical probability ⁽¹⁾ should be considered to exclude PE.</i> | IIa | B |
| <i>D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay.</i> | III | A |

(1) D-dimer cut-off levels adapted to clinical probability according to the **YEARS** model (signs of DVT, haemoptysis, and whether an alternative diagnosis is less likely than PE) may be used. According to this model, PE is excluded in patients without clinical items and D-dimer levels < 1000 mg/L, or in patients with one or more clinical items and D-dimer levels < 500 mg/L.

| | | |
|---|------------|----------|
| CTPA: | | |
| <i>It is recommended to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or who is PE-unlikely.</i> | I | A |
| <i>It should be considered to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with high clinical probability or who is PE-likely.</i> | IIa | B |
| <i>It is recommended to accept the diagnosis of PE (without further testing) if CTPA shows a segmental or more proximal filling defect in a patient with intermediate or high clinical probability.</i> | I | B |
| <i>Further imaging tests to confirm PE may be considered in cases of isolated subsegmental filling defects.</i> | IIb | C |
| <i>CT venography is not recommended as an adjunct to CTPA.</i> | III | B |
| V/Q scintigraphy: | | |
| <i>It is recommended to reject the diagnosis of PE (without further testing) if the perfusion lung scan is normal.</i> | I | A |
| <i>It should be considered to accept that the diagnosis of PE (without further testing) if the V/Q scan yields high probability for PE.</i> | IIa | B |
| <i>A non-diagnostic V/Q scan should be considered as exclusion of PE when combined with a negative proximal CUS in patients with low clinical probability, or who are PE-unlikely.</i> | IIa | B |
| V/Q SPECT: | | |
| <i>V/Q SPECT may be considered for PE diagnosis.</i> | IIb | B |
| Lower-limb CUS: | | |
| <i>It is recommended to accept the diagnosis of VTE (and PE) if a CUS shows a proximal DVT in a patient with clinical suspicion of PE.</i> | I | A |
| <i>If CUS shows only a distal DVT, further testing should be considered to confirm PE.</i> | IIa | B |
| <i>If a positive proximal CUS is used to confirm PE, assessment of PE severity should be considered to permit risk-adjusted management.</i> | IIa | C |

MRA:

MRA is not recommended for ruling out PE.

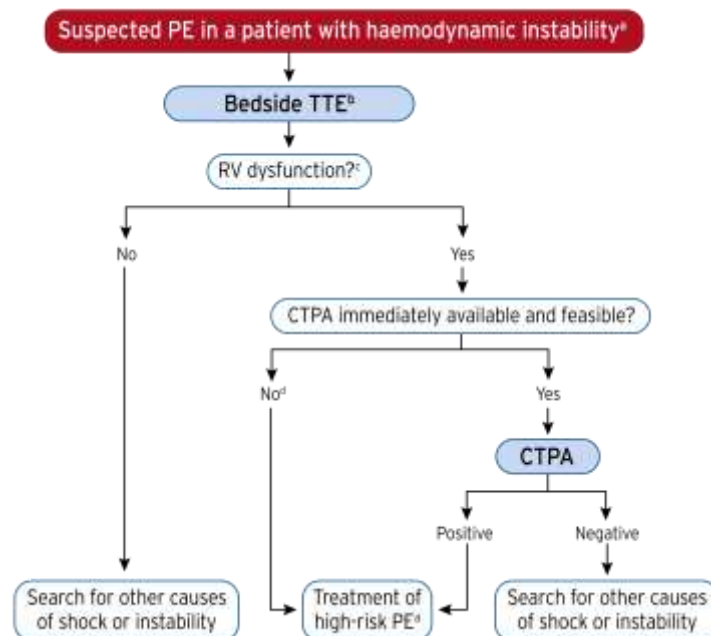
III**A**

Figure 23-3: Diagnostic algorithm for patients with suspected high-risk pulmonary embolism presenting with haemodynamic instability. B) Ancillary bedside imaging tests may include TOE, which may detect emboli in the pulmonary artery and its main branches; and bilateral venous CUS, which may confirm DVT and thus VTE. **C)** In the emergency situation of suspected high-risk PE, this refers mainly to a RV/LV diameter ratio >1.0 . **D)** Includes the cases in which the patient's condition is so critical that it only allows bedside diagnostic tests. In such cases, echocardiographic findings of RV dysfunction confirm high-risk PE and emergency reperfusion therapy is recommended. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

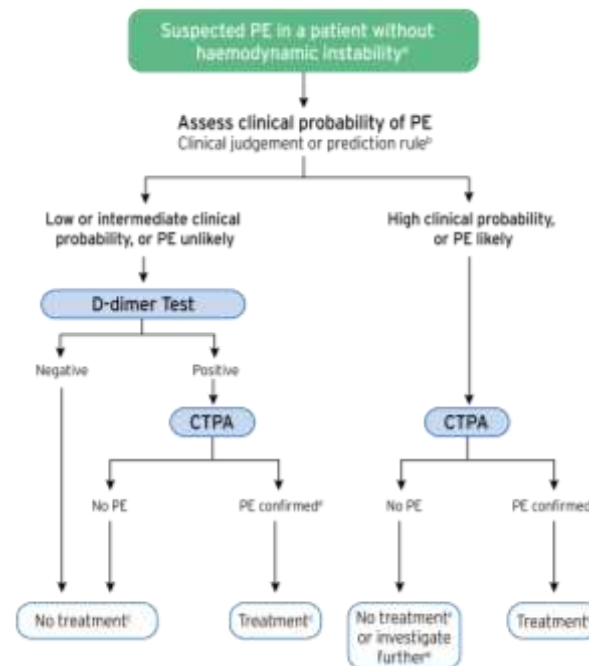


Figure 23-4: Diagnostic algorithm for patients with suspected pulmonary embolism without haemodynamic instability. **B)** Two alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE due to a higher sensitivity and negative predictive value. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients. **C)** Treatment refers to anticoagulation treatment for PE. **D)** CTPA is considered diagnostic of PE if it shows PE at the segmental or more proximal level. **E)** In case of a negative CTPA in patients with high clinical probability, investigation by further imaging tests may be considered before withholding PE-specific treatment. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

PE Risk assessment:

Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management approach. Initial risk stratification is based on clinical symptoms and signs of hemodynamic instability, which indicate a high risk of early death. In the large remaining group of patients with PE who present without hemodynamic instability, further (advanced) risk stratification requires the assessment of two sets of prognostic criteria: **(i)** clinical, imaging, and laboratory indicators of PE severity, mostly related to the presence of RV dysfunction; and **(ii)** presence of comorbidity and any other aggravating conditions that may adversely affect early prognosis.

Of the clinical scores integrating PE severity and comorbidity, the Pulmonary Embolism Severity Index (PESI) is the one that has been most extensively validated to date.

Table 23-6: Original and simplified Pulmonary Embolism Severity Index

| Parameter | Original version | Simplified version |
|------------------------------|---------------------|--------------------------------------|
| Age | <i>Age in years</i> | <i>1 point (if age >80 years)</i> |
| Male sex | <i>+10 points</i> | - |
| Cancer | <i>+30 points</i> | <i>1 point</i> |
| Chronic heart failure | <i>+10 points</i> | <i>1 point</i> |
| Chronic pulmonary disease | <i>+10 points</i> | - |
| Pulse rate ≥ 110 b.p.m. | <i>+20 points</i> | <i>1 point</i> |
| Systolic BP < 100 mmHg | <i>+30 points</i> | <i>1 point</i> |
| Respiratory rate > 30 | <i>+20 points</i> | - |
| Temperature < 36 | <i>+20 points</i> | - |
| Altered mental status | <i>+60 points</i> | - |

| | | |
|------------------------|---|---|
| SaO ₂ < 90% | +20 points | 1 point |
| Risk strata | | |
| | <ul style="list-style-type: none"> • Class I: 65 points very low 30-day mortality risk (1.6%) • Class II: 66-85 points low mortality risk (1.7-3.5%) • Class III: 86-105 points moderate mortality risk (3.2-7.1%) • Class IV: 106-125 points high mortality risk (4.0-11.4%) • Class V: >125 points very high mortality risk (10.0-24.5%) | <ul style="list-style-type: none"> • 0 points = 30 day mortality risk 1.0% (95% CI 0.0-2.1%) • ≥1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5-13.2%) |

▪ Scores for advanced risk stratification:

| Table 23-7: Scores for advanced stratification of PE-related risk in patients presenting without hemodynamic instability. | | | |
|---|--------------|--|--------------|
| Bova score Parameter | | FAST score | |
| Item | Score points | Item | Score points |
| Elevated cardiac troponin | 2 | H-FABP ≥ 6 ng/mL ⁽¹⁾ or elevated troponin | 1.5 |
| RV dysfunction (TTE or CTPA) | 2 | Syncope | 1.5 |
| Heart rate ≥ 110 b.p.m. | 1 | Heart rate ≥100 b.p.m. | 2 |

1) Heart-type fatty acid binding protein (H-FABP) is a cytosolic protein that is released rapidly from the cardiomyocyte in response to myocardial injury.

| | | | |
|-------------------------------|----------------------|----------------------|--|
| Systolic BP 90-100 mmHg | 2 | | |
| Risk classes | | | |
| | Bova score | FAST score | |
| Low risk | <i>0-2 points</i> | <i>< 3 points</i> | |
| Intermediate-low risk | <i>3-4 points</i> | <i>3-4 points</i> | |
| Intermediate-high risk | <i>> 4 points</i> | <i>≥ 3 points</i> | |

Table 23-8: Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death

| Indicators of risk | | | | |
|-----------------------------|---|--------------------------------------|--------------------------------------|--|
| Early mortality risk | Hemodynamic instability ⁽¹⁾ | PESI class III–V or sPESI ≥ 1 | RV dysfunction on TTE or CTPA | Elevated cardiac troponin levels ⁽²⁾ |
| High | + | (+) ⁽³⁾ | + | (+) |
| Intermediate-High | - | + ⁽⁴⁾ | + | + |
| Intermediate-low | - | + | One (or none) positive | |
| Low | - | - | - | if assessed, -ve |

- (1)** One of the following clinical presentations: cardiac arrest, obstructive shock (systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop ≥ 40 mmHg for > 15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).
- (2)** Elevation of further laboratory biomarkers, such as NT-proBNP ≥ 600 ng/L, H-FABP ≥ 6 ng/mL, or copeptin ≥ 24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomized controlled trials.
- (3)** Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.
- (4)** Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of III or an sPESI of 0. Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

| Table 23-9: ESC Recommendations for prognostic assessment: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>Initial risk stratification of suspected or confirmed PE, based on the presence of hemodynamic instability, is recommended to identify patients at high risk of early mortality.</i> | I | B |
| <i>In patients without hemodynamic instability, further stratification of patients with acute PE into intermediate- and low risk categories is recommended.</i> | I | B |
| <i>In patients without hemodynamic instability, use of clinical prediction rules integrating PE severity and comorbidity, preferably the PESI or sPESI, should be considered for risk assessment in the acute phase of PE.</i> | IIa | B |
| <i>Assessment of the RV by imaging methods or laboratory biomarkers should be considered, even in the presence of a low PESI or a negative sPESI.</i> | IIa | B |
| <i>In patients without hemodynamic instability, use of validated scores combining clinical, imaging, and laboratory PE-related prognostic factors may be considered to further stratify the severity of the acute PE episode.</i> | IIb | C |

Treatment in the acute phase:

▪ Hemodynamic and respiratory support:

Hypoxemia is one of the features of severe PE, and is mostly due to the mismatch between ventilation and perfusion. Administration of supplemental oxygen is indicated in patients with PE and $\text{SaO}_2 < 90\%$.

Severe hypoxemia/respiratory failure that is refractory to conventional oxygen supplementation could be explained by right-to-left shunt through a patent foramen ovale or atrial septal defect.

Further oxygenation techniques should also be considered, including high-flow oxygen (i.e. a high-flow nasal cannula) and mechanical ventilation (non-invasive or invasive in cases of extreme instability i.e. cardiac arrest), taking into consideration that correction of hypoxemia will not be possible without simultaneous pulmonary reperfusion.

Patients with RV failure are frequently hypotensive or are highly susceptible to the development of severe hypotension during induction of anaesthesia, intubation, and positive-pressure ventilation. Consequently, intubation should be performed only if the patient is unable to tolerate or cope with non-invasive ventilation. In particular, positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen low CO due to RV failure in patients with high-risk PE; therefore, positive end-expiratory pressure should be applied with caution. Tidal volumes of approximately 6 mL/kg lean body weight should be used in an attempt to keep the end-inspiratory plateau pressure < 30 cmH₂O. If intubation is needed, anesthetic drugs known to cause hypotension should be avoided for induction.

| Table 23-10: Treatment of right ventricular failure in acute high-risk pulmonary embolism | | |
|--|--|--|
| Strategy | Properties and use | Caveats |
| Volume optimization: | | |
| Cautious volume loading, saline, or Ringer's lactate, ≤ 500 mL over 15-30 min | <i>Consider in patients with normal low central venous pressure (due, for example, to concomitant hypovolemia)</i> | <i>Volume loading can overdilate the RV, worsen ventricular interdependence, and reduce CO</i> |
| Vasopressors and inotropes ⁽¹⁾ | | |
| Norepinephrine, 0.2-1 mcg/kg/min | <i>Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient</i> | <i>Excessive vasoconstriction may worsen tissue perfusion</i> |

(1) Epinephrine is used in cardiac arrest.

| | | |
|---|--|--|
| Dobutamine, 2-20 mcg/kg/min | <i>Increases RV inotropy, lowers filling pressures</i> | <i>May aggravate arterial hypotension if used without a vasopressor; may trigger/aggravate arrhythmias</i> |
| Mechanical circulatory support: | | |
| <i>Venoarterial ECMO/ extracorporeal life support</i> | <i>Rapid short-term support combined with oxygenator</i> | <i>Complications with use over longer periods (> 5-10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team</i> |

▪ **Initial anticoagulation:**

In patients with high or intermediate clinical probability of PE, anticoagulation should be initiated while awaiting the results of diagnostic tests. This is usually done with subcutaneous, weight-adjusted low-molecular weight heparin (LMWH) or fondaparinux, or i.v. unfractionated heparin (UFH). An equally rapid anticoagulant effect can also be achieved with a nonvitamin K antagonist oral anticoagulant (NOAC).

| Table 23-11: LMWH and Fondaparinux for the treatment of PE: | | |
|--|---|----------------------------------|
| | Dosage | Interval |
| Enoxaparin | <i>1.0 mg/kg <u>or</u> 1.5 mg/kg ⁽¹⁾</i> | <i>Every 12 h Once daily</i> |
| Tinzaparin | <i>175 U/kg</i> | <i>Once daily</i> |

(1) Once-daily injection of enoxaparin at a dosage of 1.5 mg/kg is approved for inpatient (hospital) treatment of PE in the USA and in some, but not all, European countries.

| | | |
|----------------------------------|--|--------------------------|
| Dalteparin | 100 IU/kg ⁽¹⁾ or 200 IU/kg | Every 12 h Once daily |
| Nadroparin ⁽²⁾ | 86 IU/kg or 171 IU/kg | Every 12 h Once daily |
| Fondaparinux | - 5 mg (body weight < 50 kg); - 7.5 mg (body weight 50-100 kg); - 10 mg (body weight > 100 kg) | Once daily |

Table 23-12: Adjustment of unfractionated heparin dosage:

| aPTT | Change of dosage |
|---------------------------|--|
| < 35 s (<1.2 control) | 80 U/kg bolus, increase infusion rate by 4 U/kg/h |
| 35-45 s (1.2-1.5 control) | 40 U/kg bolus, increase infusion rate by 2 U/kg/h |
| 46-70 s (1.5-2.3 control) | No change |
| 71-90 s (2.3-3.0 control) | Reduce infusion rate by 2 U/kg/h |
| > 90 s (>3.0 control) | Stop infusion for 1 h, then reduce infusion rate by 3 U/kg/h |

▪ **Reperfusion treatment:**

• **Systemic thrombolysis:**

Thrombolytic therapy leads to faster improvements in pulmonary obstruction, PAP, and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography. The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients

(1) In patients with cancer, dalteparin is given at a dose of 200 IU/kg body weight (maximum, 18 000 IU) once a day over a period of 1 month, followed by 150 IU/kg once a day for 5 months.

(2) Nadroparin is approved for treatment of PE in some, but not all, European countries.

who have had symptoms for 6-14 days. Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 h, has been reported in 8% of high-risk PE patients.

In normotensive patients with intermediate-risk PE, thrombolytic therapy was associated with a significant reduction in the risk of hemodynamic decompensation or collapse, but this was paralleled by an increased risk of severe extracranial and intracranial bleeding with no reduction in the risk of death.

Table 23-13: Thrombolytic regimens, doses, and contraindications:

| Molecule | Regimen |
|----------------------|---|
| rtPA | 100 mg over 2 h 0.6mg/kg over 15 min (max dose 50mg) ⁽¹⁾ |
| Streptokinase | 250.000 IU as a loading dose over 30 min, followed by 100.000 IU/h over 12-24 h Accelerated regimen: 1.5 million IU over 2 h |
| Urokinase | 4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12-24 h Accelerated regimen: 3 million IU over 2 h |

- **Percutaneous catheter-directed treatment:**

Mechanical reperfusion is based on the insertion of a catheter into the pulmonary arteries via the femoral route. Different types of catheters are used for mechanical fragmentation, thrombus aspiration, or more commonly a pharmacomechanical approach combining mechanical or ultrasound fragmentation of the thrombus with in situ reduced-dose thrombolysis.

- **Surgical embolectomy:**

(1) This is the accelerated regimen for rtPA in pulmonary embolism; it is not officially approved, but it is sometimes used in extreme hemodynamic instability such as cardiac arrest.

Surgical embolectomy in acute PE is usually carried out with cardiopulmonary bypass, without aortic cross clamping and cardioplegic cardiac arrest, followed by incision of the two main pulmonary arteries with the removal or suction of fresh clots. Recent experience appears to support combining ECMO with surgical embolectomy, particularly in patients with high-risk PE with or without the need for CPR.

▪ **Vena cava filters:**

The aim of vena cava interruption is to mechanically prevent venous clots from reaching the pulmonary circulation. Most devices in current use are inserted percutaneously and can be retrieved after several weeks or months, or left in place over the long-term, if needed.

Potential indications include VTE and absolute contraindication to anticoagulant treatment, recurrent PE despite adequate anticoagulation, and primary prophylaxis in patients with a high risk of VTE. Complications associated with vena cava filters are common and can be serious.

| Table 23-14: ESC Recommendations for inferior vena cava filters: | | |
|--|------------|----------|
| Recommendations | Class | Level |
| <p><i>IVC filters should be considered in:</i></p> <ul style="list-style-type: none"> - <i>Acute PE and absolute contraindications to anticoagulation.</i> - <i>PE recurrence despite therapeutic anticoagulation.</i> | IIa | C |
| <i>Routine use of IVC filters is not recommended.</i> | III | A |

Treatment strategies:

• **Emergency treatment of high-risk PE:**

Primary reperfusion treatment, in most cases systemic thrombolysis, is the treatment of choice for patients with high-risk PE. Surgical pulmonary embolectomy or percutaneous catheter-directed treatment are alternative reperfusion options in patients with contraindications to thrombolysis, if expertise with either of these methods and the appropriate resources are available on-site.

• **Treatment of intermediate-risk PE:**

For most cases of acute PE without hemodynamic compromise, parenteral or oral anticoagulation (without reperfusion techniques) is adequate treatment. Routine primary reperfusion treatment, notably full-dose systemic thrombolysis, is not recommended, as the risk of potentially life-threatening bleeding complications appears too high for the expected benefits from this treatment. Rescue thrombolytic therapy or, alternatively, surgical embolectomy or percutaneous catheter-directed treatment should be reserved for patients who develop signs of hemodynamic instability.

• **Management of low-risk PE: triage for early discharge and home treatment:**

Early discharge of a patient with acute PE and continuation of anticoagulant treatment at home should be considered if three sets of criteria are fulfilled: (i) the risk of early PE-related death or serious complications is low; (ii) there is no serious comorbidity or aggravating condition(s) that would mandate hospitalization; and (iii) proper outpatient care and anticoagulant treatment can be provided.

| Table 23-15: Hestia exclusion criteria for outpatient management: |
|---|
| Criterion/question |
| Is the patient hemodynamically unstable? ⁽¹⁾ |

(1) Include the following criteria but leave them to the discretion of the investigator: systolic BP <100 mmHg with heart rate >100 b.p.m; condition requiring admission to an intensive care unit.

Is thrombolysis or embolectomy necessary?

Active bleeding or high risk of bleeding? ⁽¹⁾

More than 24 h of oxygen supply to maintain oxygen saturation >90%?

Is PE diagnosed during anticoagulant treatment?

Severe pain needing i.v. pain medication for more than 24 h?

Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, or no support system)?

Does the patient have a CrCl of <30 mL/min? ⁽²⁾

Does the patient have severe liver impairment? ⁽³⁾

Is the patient pregnant?

Does the patient have a documented history of heparin-induced thrombocytopenia?

If the answer to one or more of the questions is 'yes', then the patient cannot be treated at home.

(1) *Gastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count <75-109/L), or uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP > 110 mmHg).*

(2) *Calculated CrCl according to the CockcroftGault formula.*

(3) *Left to the discretion of the physician.*

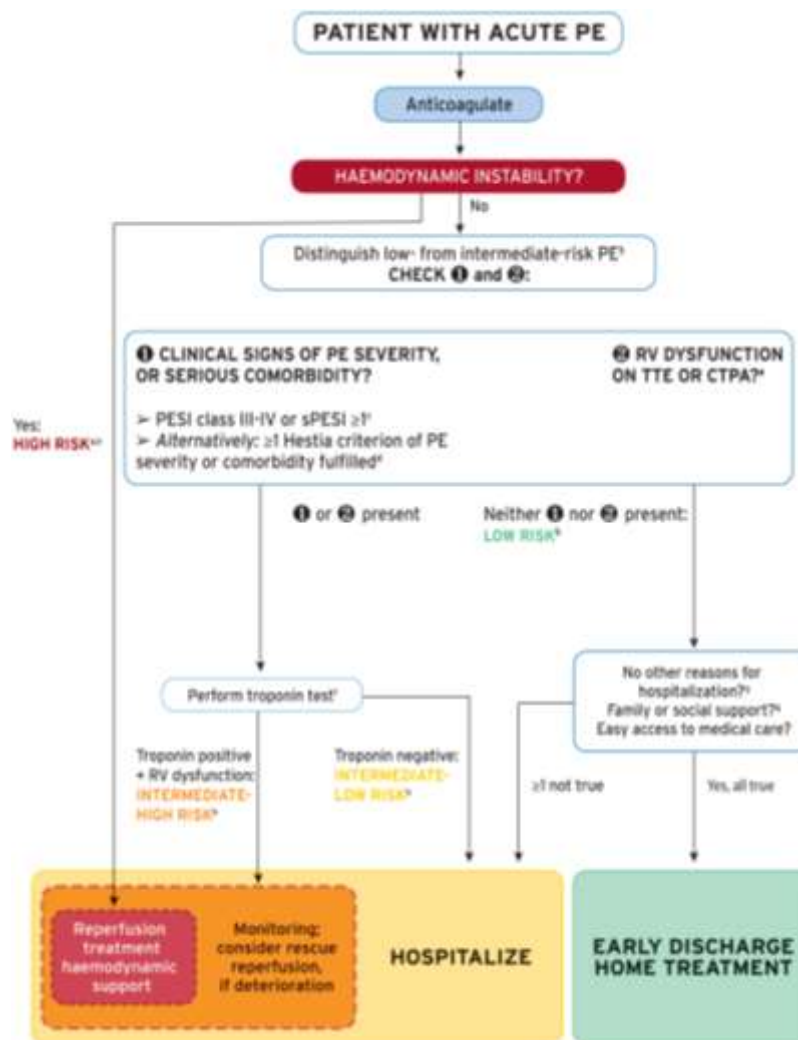


Figure 23-5: Central Illustration. Risk-adjusted management strategy for acute pulmonary embolism. PESI = Pulmonary Embolism Severity Index; sPESI = simplified Pulmonary Embolism Severity Index. **C)** Cancer, heart failure and chronic lung disease are included in the PESI and sPESI. **F)** A cardiac troponin test may already have been performed during initial diagnostic work-up. **G)** Included in the Hestia criteria. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

| Table 23-16: ESC Recommendations for acute-phase treatment of pulmonary embolism: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| High-risk pulmonary embolism: | | |
| <i>It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.</i> | I | C |
| <i>Systemic thrombolytic therapy is recommended for high-risk PE.</i> | I | B |
| <i>Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.</i> | I | C |
| <i>Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.</i> | IIa | C |
| <i>Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.</i> | IIa | C |
| <i>ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.</i> | IIb | C |
| Intermediate- or low-risk pulmonary PE: | | |
| Initiation of anticoagulation | | |
| <i>Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic workup is in progress.</i> | I | C |
| <i>If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.</i> | I | A |
| <i>When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.</i> | I | A |

| | | |
|--|------------|----------|
| <i>When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2:3) is reached.</i> | I | A |
| <i>NOACs are not recommended in patients with severe renal impairment ⁽¹⁾, during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome.</i> | III | C |
| Reperfusion treatment | | |
| <i>Rescue thrombolytic therapy is recommended for patients with hemodynamic deterioration on anticoagulation treatment.</i> | I | B |
| <i>As an alternative to rescue thrombolytic therapy, surgical embolectomy or percutaneous catheter-directed treatment should be considered for patients with hemodynamic deterioration on anticoagulation treatment.</i> | IIa | C |
| <i>Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE ⁽²⁾.</i> | III | B |
| Early discharge and home treatment: | | |
| <i>Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided.</i> | IIa | A |

(1) Dabigatran is not recommended in patients with CrCl <30 mL/min. Edoxaban should be given at a dose of 30 mg once daily in patients with CrCl of 15-50 mL/min and is not recommended in patients with CrCl <15 mL/min. Rivaroxaban and apixaban are to be used with caution in patients with CrCl 15-29 mL/min, and their use is not recommended in patients with CrCl <15 mL/min.

(2) The risk-to-benefit ratios of surgical embolectomy or catheter-directed procedures have not yet been established in intermediate- or low-risk PE.

Chronic treatment and prevention of recurrence:

The aim of anticoagulation after acute PE is to complete the treatment of the acute episode and prevent recurrence of VTE over the long-term. Oral anticoagulants are highly effective in preventing recurrent VTE during treatment, but they do not eliminate the risk of subsequent recurrence after the discontinuation of treatment. Based on this fact on the one hand, and considering the bleeding risk of anticoagulation treatment on the other, the clinically important question is how to best select candidates for extended or indefinite anticoagulation.

▪ **Assessment of venous thromboembolism recurrence risk:**

Patients can be classified into distinct groups based on their risk of VTE recurrence after discontinuation of anticoagulant treatment:

- 1) Patients in whom a strong (major) transient or reversible risk factor, most commonly major surgery or trauma, can be identified as being responsible for the acute (index) episode;
- 2) Patients in whom the index episode might be partly explained by the presence of a weak (minor) transient or reversible risk factor, or if a non-malignant risk factor for thrombosis persists;
- 3) Patients in whom the index episode occurred in the absence of any identifiable risk factor (the ESC guidelines avoid terms such as ‘unprovoked’ or ‘idiopathic’ VTE);
- 4) Patients with one or more previous episodes of VTE, and those with a major persistent pro-thrombotic condition such as antiphospholipid antibody syndrome; and
- 5) Patients with active cancer.

Table 23-17: Categorization of risk factors for VTE based on the risk of recurrence over the long term ⁽¹⁾:

(1) If anticoagulation is discontinued after the first 3 months.

| Estimated risk for long term recurrence ⁽¹⁾ | Risk factor category for index PE ⁽²⁾ | Examples |
|--|--|---|
| Low (< 3% per year) | <i>Major transient or reversible factors associated with > 10-fold increased risk for the index VTE event (compared to patients without the risk factors)</i> | <ul style="list-style-type: none"> - Surgery with general anaesthesia for > 30 min. - Confined to bed in hospital (only bathroom privileges) for ≥ 3 days due to an acute illness. Or acute exacerbation of a chronic illness - Trauma with fractures |
| Intermediate (3-8%) | <ul style="list-style-type: none"> - Transient or reversible factors associated with ≤ 10-fold increased risk for first (index) VTE - Non malignant persistent risk factors - No identifiable risk factor | <ul style="list-style-type: none"> - Minor surgery (general anaesthesia for < 30 min.) - Admission to hospital for < 3 days with an acute illness - Oestrogen therapy/contraception - Pregnancy or puerperium - Confined to bed out of hospital for ≥ 3 days with an acute illness - Leg injury (without fracture) associated with reduced mobility for ≥ 3 days - Long-haul flight - Inflammatory bowel disease - Active autoimmune disease |
| High (> 8% per year) | | <ul style="list-style-type: none"> - Active cancer - One or more previous episodes of VTE in the absence of a major transient or reversible factor |

(1) If anticoagulation is discontinued after the first 3 months

(2) The present guidelines avoid terms such as “provoked”, “unprovoked”, or “idiopathic” VTE.

Overall, assessment of the VTE recurrence risk after acute PE, in the absence of a major transient or reversible risk factor, is a complex issue. Beyond the examples listed in the table above, patients who are carriers of some forms of hereditary thrombophilia, notably those with confirmed deficiency of antithrombin, protein C, or protein S, and patients with homozygous factor V Leiden or homozygous prothrombin G20210A mutation, are often candidates for indefinite anticoagulant treatment after a first episode of PE occurring in the absence of a major reversible risk factor. In view of these possible implications, testing for thrombophilia (including antiphospholipid antibodies and lupus anticoagulant) may be considered in patients in whom VTE occurs at a young age (e.g. aged < 50 years) and in the absence of an otherwise identifiable risk factor, especially when this occurs against the background of a strong family history of VTE.

On the other hand, no evidence of a clinical benefit of extended anticoagulant treatment is currently available for carriers of heterozygous factor V Leiden or prothrombin 20210A mutation.

▪ **Anticoagulant-related bleeding risk:**

The risk of major bleeding is higher in the first month of anticoagulant treatment, and then declines and remains stable over time. Based on currently available evidence, risk factors include:

- Advanced age (particularly >75 years);
- Previous bleeding (if not associated with a reversible or treatable cause) or anaemia;
- Active cancer;
- Previous stroke, either hemorrhagic or ischemic;
- Chronic renal or hepatic disease;
- Concomitant antiplatelet therapy or NSAIDs (to be avoided, if possible);
- Other serious acute or chronic illness; and
- Poor anticoagulation control.

Table 23-18: ESC Recommendations for the regimen and duration of anticoagulation after pulmonary embolism in patients without cancer:

| Recommendations | Class | Level |
|--|--|----------------------------------|
| <i>Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE.</i> | I | A |
| Anticoagulation for only 3 months: | | |
| <i>For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months.</i> | I | B |
| Anticoagulation beyond 3 months: | | |
| <i>Oral anticoagulant treatment of indefinite duration is recommended for:</i> <i>- Patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor.</i> <i>- Patients with antiphospholipid antibody syndrome (using only VKA).</i> | I | B |
| <i>Extended oral anticoagulation of indefinite duration should be considered for ⁽¹⁾:</i> <i>- Patients with a first episode of PE and no identifiable risk factor.</i> <i>- Patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome.</i> <i>- Patients with a first episode of PE associated with a minor transient or reversible risk factor.</i> | IIa IIa IIa | A C C |
| NOAC dose in extended anticoagulation ⁽²⁾ | | |

(1) The patient's bleeding risk should be assessed to identify and treat modifiable bleeding risk factors, and it may influence decision-making on the duration and regimen/dose of anticoagulant treatment.

(2) If dabigatran or edoxaban is chosen for extended anticoagulation after PE, the dose should remain unchanged, as reduced-dose regimens were not investigated in dedicated extension trials.

| | | |
|---|------------|----------|
| <i>If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation.</i> | IIa | A |
| Extended treatment with alternative antithrombotic agents | | |
| <i>In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.</i> | IIb | B |
| Follow-up of the patient under anticoagulation | | |
| <i>In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal function ⁽¹⁾, and bleeding risk be reassessed at regular intervals.</i> | I | C |

Follow up and Long-term sequelae of pulmonary embolism:

The patency of the pulmonary arterial bed is restored in the majority of PE survivors within the first few months following the acute episode; therefore, no routine follow-up CTPA imaging is needed in such patients treated for PE. However, in other patients, thrombi become persistent and organized, which in rare cases may result in CTEPH, a potentially life-threatening obstructing vasculopathy. The rarity of this condition is in contrast to the relatively large number of patients who report persisting dyspnoea or poor physical performance over several months after acute PE.

▪ **Persisting symptoms and functional limitation after PE:**

Persisting or deteriorating dyspnoea, and poor physical performance, are frequently present 6 months to 3 years after an acute PE episode. The proportion of patients claiming that their health status is worse at 6-month follow-up than it was at the time of PE diagnosis varies widely, ranging between 20 and 75%. Muscle deconditioning, particularly in the presence of excess body

(1) Especially for patients receiving NOACs.

weight and cardiopulmonary comorbidity, is largely responsible for the frequently reported dyspnea and signs of exercise limitation after acute PE.

▪ **Chronic thromboembolic pulmonary hypertension (CTEPH):**

CTEPH is a disease caused by the persistent obstruction of pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodelling of the pulmonary microvascular bed.

CTEPH has been reported with a cumulative incidence of between 0.1 and 9.1% in the first 2 years after a symptomatic PE event; the large margin of error is due to referral bias, the paucity of early symptoms, and the difficulty of differentiating acute PE from symptoms of preexisting CTEPH.

Table 23-19: Risk factors and predisposing conditions for CTEPH:

| Findings related to the acute PE event (obtained at PE diagnosis) | Chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3-6 month follow-up) |
|--|---|
| <ul style="list-style-type: none"> ○ <i>Previous episodes of PE or DVT</i> ○ <i>Large pulmonary arterial thrombi on CTPA</i> ○ <i>Echocardiographic signs of PH/RV dysfunction</i> ○ <i>CTPA findings suggestive of pre-existing CTEPD</i> | <ul style="list-style-type: none"> ○ <i>Ventriculo-atrial shunts</i> ○ <i>Infected chronic i.v. lines or pacemakers</i> ○ <i>History of splenectomy</i> ○ <i>Thrombophilic disorders, particularly antiphospholipid syndrome and high coagulation factor VIII levels</i> ○ <i>Non-O blood group</i> ○ <i>Hypothyroidism treated with thyroid hormones</i> ○ <i>History of cancer</i> ○ <i>Myeloproliferative disorders</i> ○ <i>Inflammatory bowel disease</i> ○ <i>Chronic osteomyelitis</i> |

Table 23-20: Findings of pre-existing CTEPH on CT pulmonary angiography:

Direct vascular signs:

- *Eccentric wall-adherent filling defect(s), which may calcify; different from the central filling defects within a distended lumen, which are the hallmark of acute PE.*
- *Abrupt tapering and truncation.*
- *Complete occlusion and pouch defects.*
- *Intimal irregularity.*
- *Linear intraluminal filling defects (intravascular webs and bands).*
- *Stenosis and post-stenotic dilatation.*
- *Vascular tortuosity.*

Indirect vascular signs:

- *Significant RV hypertrophy, RA dilatation.*
- *Pericardial effusion.*
- *Dilatation of pulmonary artery (> 29 mm in men and > 27 mm in women) and/or calcifications of pulmonary artery.*
- *Systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post obstructive vessels).*

Parenchymal changes:

Mosaic attenuation of the lung parenchyma resulting in geographical variation in perfusion.

Table 23-21: ESC Recommendations for follow-up after acute pulmonary embolism

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|---|------------|----------|
| <i>Routine clinical evaluation ⁽¹⁾ of patients 3-6 months after the acute PE episode is recommended.</i> | I | B |
| <i>An integrated model of patient care after PE (involving hospital specialists, appropriately qualified nurses, and primary care physicians) is recommended to ensure optimal transition from hospital to community care.</i> | I | C |
| <i>In symptomatic patients with mismatched perfusion defects persisting on V/Q scan ⁽²⁾ beyond 3 months after acute PE, referral to a PH/CTEPH expert centre is recommended, after taking into account the results of echocardiography, natriuretic peptide levels, and/or CPET.</i> | I | C |
| <i>Further diagnostic evaluation should be considered in patients with persistent or new onset dyspnoea/exercise limitation after PE.</i> | IIa | C |
| <i>Further diagnostic evaluation may be considered in asymptomatic patients with risk factors for CTEPH.</i> | IIb | C |

(1) For symptoms suggesting recurrence, bleeding, malignancy, or persistent or new-onset exercise limitation, and to decide on extension of anticoagulant treatment.

(2) Alternatively, dual-energy CT may be used, if appropriate expertise and resources are available on-site.

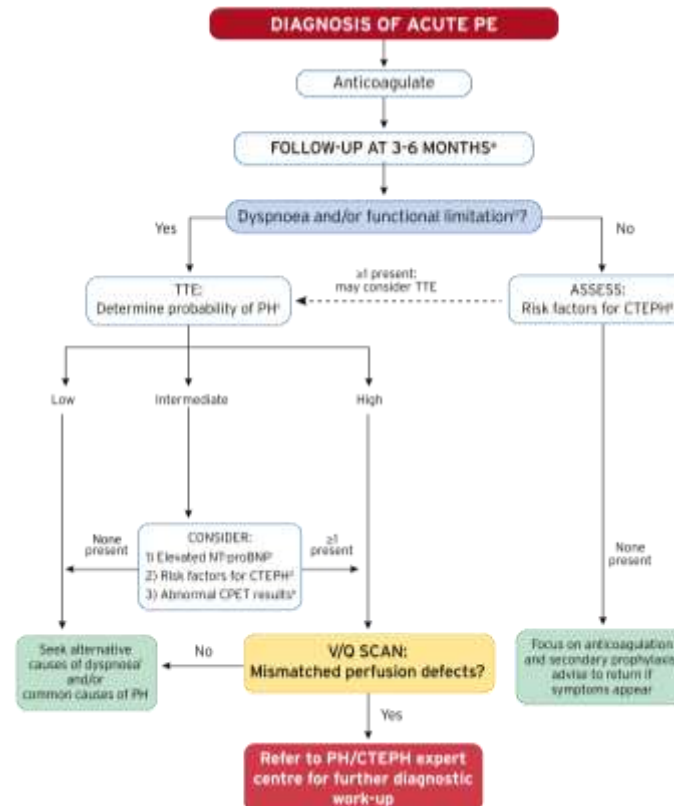


Figure 23-6: Follow-up strategy and diagnostic workup for long-term sequelae of pulmonary embolism. A) Assess the persistence (or new onset) and severity of dyspnoea or functional limitation, and also check for possible signs of VTE recurrence, cancer, or bleeding complications of anticoagulation. B) The Medical Research Council scale can be used to standardize the evaluation of dyspnoea; alternatively, the WHO functional class can be determined. C) As defined by the ESC/ERS guidelines on the diagnosis and treatment of Pulmonary Hypertension. E) Abnormal results include, among others, reduced maximal aerobic capacity (peak oxygen consumption), increased ventilatory equivalent for carbon dioxide, and reduced end-tidal carbon dioxide pressure. F) Consider CPET in the diagnostic work-up. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

Management of PE in patients with cancer:

Table 23-22: ESC Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.</i> | Ila | A |
| <i>Edoxaban or Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.</i> | Ila | B |
| <i>For patients with PE and cancer, extended anticoagulation (beyond the first 6 months) should be considered for an indefinite period or until the cancer is cured.</i> | Ila | B |
| <i>In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.</i> | Ila | B |

Pulmonary embolism and pregnancy:

Acute PE remains one of the leading causes of maternal death in high-income countries. VTE risk is higher in pregnant women compared with non-pregnant women of similar age; it increases during pregnancy and reaches a peak during the post-partum period.

Diagnosis of PE during pregnancy can be challenging as symptoms frequently overlap with those of normal pregnancy. The overall prevalence of confirmed PE is low among women investigated for the disease, between 2 and 7%. Recent data suggest that a diagnostic strategy based on assessment of clinical probability, D-dimer measurement, CUS, and CTPA may safely exclude PE in pregnancy. Both maternal and fetal radiation exposure are low using modern imaging techniques.

| Table 23-23: Estimated amounts of radiation absorbed in procedures used to diagnose PE: | | |
|---|--|--|
| Test | Estimated foetal radiation exposure (mGy) ⁽¹⁾ | Estimated maternal radiation exposure to breast tissue (mGy) |
| <i>Chest X-ray</i> | < 0.01 | < 0.1 |
| <i>Perfusion lung scan with technetium-99m Labelled albumin</i> | | |
| - Low dose: 40 MBq | 0.02 - 0.20 | 0.16 - 0.5 |
| - High dose: 200 MBq | 0.20 - 0.60 | 1.2 |
| <i>Ventilation lung scan</i> | 0.10 - 0.30 | < 0.01 |
| <i>CTPA</i> | 0.05 - 0.5 | 3 – 10 |

- **Treatment of PE in pregnancy:**

LMWH is the treatment of choice for PE during pregnancy. In contrast to VKAs and NOACs, LMWH does not cross the placenta, and consequently does not confer a risk of fetal hemorrhage or teratogenicity. Moreover, while UFH is also safe in pregnancy, LMWH has more predictable pharmacokinetics and a more favourable risk profile.

(1) Absorbed radiation dose is expressed in:

- mGy to reflect the radiation exposure to single organs, or the foetus, as a result of various diagnostic techniques.
- millisieverts to reflect the effective doses of all organs that have been exposed.

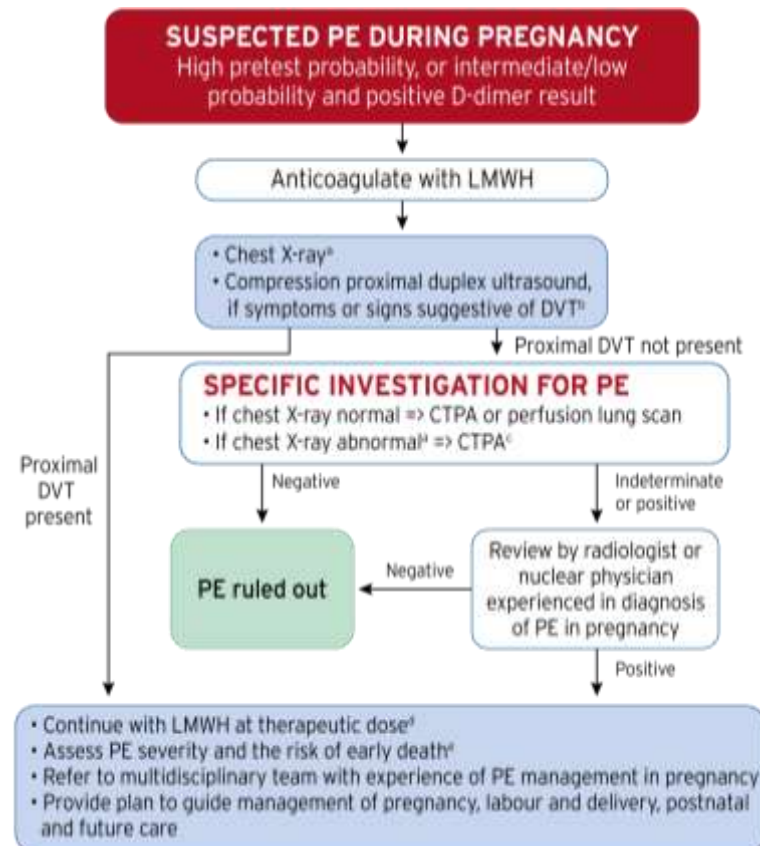


Figure 23-7: Diagnostic workup and management of suspected pulmonary embolism during pregnancy, and up to 6 weeks post-partum. CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography. **A)** If chest X-ray abnormal, consider also alternative cause of chest symptoms. **B)** DVT in pelvic veins may not be ruled out by CUS. If the entire leg is swollen, or there is buttock pain or other symptoms suggestive of pelvic thrombosis, consider magnetic resonance venography to rule out DVT. **C)** CTPA technique must ensure very low foetal radiation exposure. **D)** Perform full blood count (to measure haemoglobin and platelet count) and calculate creatinine clearance before administration. Assess bleeding risk and ensure absence of contra-indications. **Source:** 2019 ESC/ERS Guidelines for the diagnosis and management of acute pulmonary embolism.

| Table 23-24: ESC Recommendations for pulmonary embolism in pregnancy: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Diagnosis | | |
| Formal diagnostic assessment with validated methods is recommended if PE is suspected during pregnancy or in the post-partum period. | I | B |
| D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period. | IIa | B |
| In a pregnant patient with suspected PE (particularly if she has symptoms of DVT), venous CUS should be considered to avoid unnecessary irradiation. | IIa | B |
| Perfusion scintigraphy or CTPA (with a low-radiation dose protocol) should be considered to rule out suspected PE in pregnant women; CTPA should be considered as the first-line option if the chest X-ray is abnormal. | IIa | C |
| Treatment | | |
| A therapeutic, fixed dose of LMWH based on early pregnancy body weight is the recommended therapy for PE in the majority of pregnant women without hemodynamic instability. | I | B |
| Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE. | IIa | C |
| Insertion of a spinal or epidural needle is not recommended, unless ≥ 24 h have passed since the last therapeutic dose of LMWH. | III | C |
| Administration of LMWH is not recommended within 4 h of removal of an epidural catheter. | III | C |
| NOACs are not recommended during pregnancy or lactation. | III | C |

Amniotic fluid embolism

Amniotic fluid embolism should be considered in a pregnant or post-partum woman with otherwise unexplained cardiac arrest, sustained hypotension, or respiratory deterioration, especially if accompanied by disseminated intravascular coagulation.

Ila

C

Management of pulmonary embolism in specific clinical situations

Table 23-25: Management of pulmonary embolism in specific clinical situations:

| Clinical setting | Suggested management |
|---|---|
| Subsegmental PE | <ul style="list-style-type: none">• Single subsegmental PE in an outpatient without cancer and without proximal DVT: Clinical surveillance.• Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: Anticoagulant treatment.• Multiple subsegmental PE: Anticoagulant treatment. |
| Incidental PE | <ul style="list-style-type: none">• If single subsegmental PE: Proceed as above.• In all other cases: Anticoagulant treatment. |
| Acute PE with active bleeding | <ul style="list-style-type: none">• Insert IVC filter (preferably retrievable).• Reassess the possibility of anticoagulation as soon as the bleeding has ceased and the patient is stabilized, and remove the filter as soon as anticoagulant treatment is resumed. |
| PE in the elderly, frail patients, and patients with polypharmacy | <ul style="list-style-type: none">• Assess clinical probability of PE as in the non-frail patient, but caution needed in the nursing home setting as clinical prediction rules may be unreliable. |

| | |
|--|--|
| | <ul style="list-style-type: none"> • <i>Prefer NOACs over VKAs in elderly and frail patients, but avoid in patients with severe renal impairment and consider the possible interactions between NOACs and the patient's concomitant medication.</i> • <i>Reassess, at regular intervals, drug tolerance and adherence, hepatic and renal function, and the patient's bleeding risk.</i> |
| Patient with suspected 'acute-on-chronic' PE (signs of chronic pulmonary hypertension on TTE ⁽¹⁾ , or findings suggesting pre-existing CTEPH on CTPA) | <ul style="list-style-type: none"> • <i>If the diagnosis of acute PE has been confirmed, focus on the patient's acute problem and proceed to risk-adjusted acute-phase treatment of PE.</i> • <i>Perform a TTE upon discharge, and document any signs of persisting pulmonary hypertension or RV dysfunction.</i> • <i>Continue anticoagulation for ≥ 3 months and schedule the patient for a 3-month follow-up visit.</i> • <i>At the 3-month follow-up visit, assess the presence of persisting or worsening symptoms, or functional limitation, and consider further tests and possible referral to a PH/CTEPH expert centre.</i> |
| Acute PE and ESRD | <i>Administer UFH; consider anti-Xa (rather than aPTT) monitoring.</i> |
| Duration of anticoagulation in a young female patient suffering acute PE while on oral contraceptives | <ul style="list-style-type: none"> • <i>If patient was taking an oestrogen-containing contraceptive, and especially if PE occurred in the first 3 months of initiation of contraception:</i> <i>Discontinue hormonal contraceptives after discussing alternative methods of contraception; consider discontinuing anticoagulation after 3 months.</i> • <i>All other cases:</i> <i>- Manage chronic anticoagulation as after acute PE occurring in the absence of identifiable risk factors.</i> |

(1) Increased RV wall thickness or tricuspid insufficiency jet velocity beyond values compatible with acute RV pressure overload (> 3.8 m/s or a tricuspid valve peak systolic gradient >60 mmHg).

| | |
|--|--|
| | <ul style="list-style-type: none"> - Consider using a validated prediction model for quantification of the risk for VTE recurrence; for example, the HERDOO2 ⁽¹⁾ score. A score of 0 or 1 may help identify young women who can safely discontinue anticoagulation. - Advise patient on the need for prophylaxis with LMWH in case of pregnancy. |
| Long-term management of PE during pregnancy | <ul style="list-style-type: none"> - Anticoagulation with LMWH throughout pregnancy and > 6 weeks post-partum. - No NOACs during pregnancy or lactation. - Advise patient on the need for prophylaxis with LMWH in future pregnancies. |
| Anticoagulation in the patient with PE and cancer, after the first 6 months | <ul style="list-style-type: none"> • If cancer still active: ⁽²⁾ Continue anticoagulation LMWH or, alternatively, edoxaban or rivaroxaban. • If cancer in remission: <ul style="list-style-type: none"> - Continue oral anticoagulation (NOAC or VKA); alternatively, consider discontinuing if the bleeding risk is high. - In either case, periodically reassess the risk benefit ratio of continuing anticoagulation. |

Non-thrombotic pulmonary embolism

Different cell types can cause non-thrombotic embolization, including adipocytes, hematopoietic, amniotic, trophoblastic, and tumor cells. In addition, bacteria, fungi, parasites, foreign materials, and gas can lead to PE. Symptoms are similar to those of acute VTE and include dyspnoea, tachycardia, chest pain, cough, and occasionally hemoptysis, cyanosis, and syncope.

Diagnosis of non-thrombotic PE can be a challenge. In the case of small particles, microemboli cannot be detected on CT images. Given the rarity of this disease, clinical evidence is limited and mainly based on small case series.

• Septic embolism:

(1) **HERDOO2**= Hyperpigmentation, Edema, or Redness in either leg; D-dimer ≥ 250 Ig/L; Obesity (BMI ≥ 30); or Older (age ≥ 65 years)

(2) Recurrent, regionally advanced, or metastatic cancer; cancer for which treatment has been administered in the past 6 months; or haematological cancer that is not in complete remission.

Septic embolism to the pulmonary circulation is a relatively rare clinical event and is commonly associated with right-sided endocarditis. Risk factors include intravenous drug abuse and infected indwelling catheters or pacemaker wires.

- **Foreign-material pulmonary embolism:**

The increasing use of interventional techniques in modern medicine has drastically increased the incidence of foreign-material PE. Examples of foreign material include silicone, broken catheters, guide wires, vena cava filters, coils for embolization, and endovascular stent components.

- **Fat embolism:**

Embolization of fat occurs in almost all patients with pelvic or long bone fractures and in those undergoing endomedullary nailing or placement of knee and hip prostheses, but also during lipid and propofol infusion, intra-osseous infusion and bone marrow harvest, and in sickle cell disease, fatty liver disease, pancreatitis, and after liposuction.

The classical triad of fat embolization is characterized by *altered mental status, respiratory distress, and petechial rash* occurring typically 12-36 hours after injury.

- **Air embolism:**

Although air embolism can occur in both the venous and arterial systems, venous emboli are more common. Venous air embolization is often an iatrogenic complication of the manipulation of central venous and hemodialysis catheters.

The lethal volume of air after injection in humans is estimated to range from 100 to 500 mL.

The major effect of venous air embolism is the obstruction of the RVOT, or of the pulmonary arterioles, by a mixture of air bubbles and fibrin.

- **Amniotic fluid embolism:**

Amniotic fluid embolism is a rare but catastrophic complication unique to pregnancy.

The most likely mechanism is that amniotic fluid is forced into the uterine veins during normal labour or when the placenta is disrupted by surgery or trauma. As a consequence, pulmonary vessels are obstructed by cell groups and meconium, and an inflammatory reaction occurs due to the release of active metabolites. The majority of patients develop **seizures**.

- **Tumor embolism:**

Pulmonary intravascular tumor emboli are seen in up to 26% of autopsies of patients with solid malignancies, although the diagnosis is rarely made before death.

Carcinoma of the prostate gland, digestive system, liver, and breast is most commonly implicated.

Important trials in pulmonary embolism:

Table 23-26: Clinical trials in pulmonary embolism:

| Trial (date) | Summary |
|--------------------------|---|
| PEITHO (2014) | <p>Aim: <i>To investigate the clinical efficacy and safety of fibrinolytic therapy in normotensive patients with acute pulmonary embolism and an intermediate risk of an adverse outcome.</i></p> <p>Study: <i>1005 normotensive patients with intermediate-risk pulmonary embolism (patients who had RV dysfunction on echocardiography or CT, as well as myocardial injury as indicated by a positive test for cardiac troponin I or troponin T) were randomized to receive tenecteplase plus heparin with placebo plus heparin. The primary outcome was death or hemodynamic decompensation (or collapse) within 7 days after randomization. Fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke.</i></p> |

References and suggested readings:

- Stavros V Konstantinides, Guy Meyer, Cecilia Becattini, et al., ESC Scientific Document Group, 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC), *European Heart Journal*, Volume 41, Issue 4, 21 January 2020, Pages 543–603
- Griffin, B., Callahan, T., Menon, V., Wu, W., Cauthen, C. and Dunn, J., 2018. *Manual of cardiovascular medicine*. 5th ed. Lippincott Williams & Wilkins (LWW).
- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier.

Chapter 24

Pulmonary Hypertension

Definition:

Pulmonary hypertension (PH) is a syndrome characterized by marked remodeling of the pulmonary vasculature and a progressive rise in the pulmonary vascular load, leading to RV hypertrophy and remodeling.

The definitions for PH are based on haemodynamic assessment by right heart catheterization (RHC), but the final diagnosis and classification should reflect the whole clinical context and all investigations.

Pulmonary hypertension is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest.

| Table 24-1: Hemodynamic definitions of pulmonary hypertension: | | |
|--|---|---|
| Definition | Characteristics | Clinical group(s) |
| PH | mPAP > 20 mmHg | <i>All</i> |
| Pre-capillary PH | mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR > 2 WU ⁽¹⁾ | 1) <i>Pulmonary arterial hypertension</i> 3) <i>PH due to lung diseases</i> 4) <i>Chronic thromboembolic PH</i> 5) <i>PH with unclear and/or multifactorial mechanisms</i> |
| Post-capillary PH | mPAP > 20 mmHg PAWP > 15 mmHg | 2) <i>PH due to left heart disease</i> 5) <i>PH with unclear and/or multifactorial mechanisms</i> |

(1) Wood Units are preferred to dynes.s.cm⁻⁵. To convert from Wood units to dyn.s.cm⁻⁵ you must multiply by 80.

| | | |
|---|--|--|
| Isolated post-capillary PH | PVR \leq 2 WU | |
| Combined Post-capillary and pre-capillary PH | PVR $>$ 2 WU | |
| unclassified PH | Elevated mPAP ($>$ 20 mmHg) but low PVR (\leq 2 WU) and low PAWP (\leq 15 mmHg) | |
| Exercise PH | mPAP/CO slope between rest and exercise $>$ 3 mmHg/L/min | |

Clinical classification of PH:

Table 24-2: Clinical Classification of pulmonary hypertension:

Group 1: Pulmonary arterial hypertension (PAH):

- 1.1 Idiopathic (IPAH)
 - 1.1.1 Non-responders at vasoreactivity testing
 - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable (HPAH)
- 1.3 Associated with drugs and toxins (DPAH) ⁽¹⁾
- 1.4 Associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

Group 2: PH associated with left heart disease:

- 2.1 Heart failure:
 - 2.1.1 with preserved ejection fraction
 - 2.1.2 with reduced or mildly reduced ejection fraction
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH.

Group 3: PH associated with lung diseases and/or hypoxia:

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g., high altitude)
- 3.6 Developmental lung disorders

Group 4: PH associated with pulmonary artery obstructions:

- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions ⁽²⁾

Group 5: PH with unclear and/or multifactorial mechanisms:

- 5.1 Haematological disorders ⁽³⁾
- 5.2 Systemic disorders ⁽⁴⁾

(1) Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders.

Drugs definitely associated with PAH: Aminorex, Benfluorex, Dasatinib, Dexfenfluramine, Fenfluramine, Methamphetamines, and Toxic rapeseed oil.

Drugs possibly associated with PAH: Alkylating agents (cyclophosphamide, mitomycin C), Amphetamines, Bosutinib, Cocaine, Diazoxide, Direct-acting antiviral agents against HCV (sofosbuvir), Indirubin (Chinese herb Qing-Dai), Interferon alpha and beta, Leflunomide, L-tryptophan, Phenylpropanolamine, Ponatinib, Selective proteasome inhibitors (carfilzomib), Solvents (trichloroethylene), St John's Wort.

(2) Other causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumours (e.g., renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), non-malignant tumours (e.g., uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis.

(3) Including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders.

(4) Including sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1.

5.3 Metabolic disorders ⁽¹⁾

5.4 Chronic renal failure with or without haemodialysis

5.5 Pulmonary tumour thrombotic microangiopathy ⁽²⁾

5.6 Fibrosing mediastinitis ⁽³⁾

Globally, left heart disease (LHD) is the leading cause of PH. Lung disease, especially COPD, is the second most common cause.

(1) Including glycogen storage diseases and Gaucher disease.

(2) It is a fatal disease process in which tumor cells embolize to the pulmonary vasculature; there is activation of the coagulation cascade, formation of fibrin clots, and fibrocellular proliferation of the intimal layer of blood vessel walls. The most commonly reported malignancy is gastric adenocarcinoma.

(3) It is characterized by invasive, calcified fibrosis centered on lymph nodes that block major vessels and airways. In Europe, this disease is exceptionally rare. More cases are seen in USA where the disease may often be associated with **histoplasmosis**.

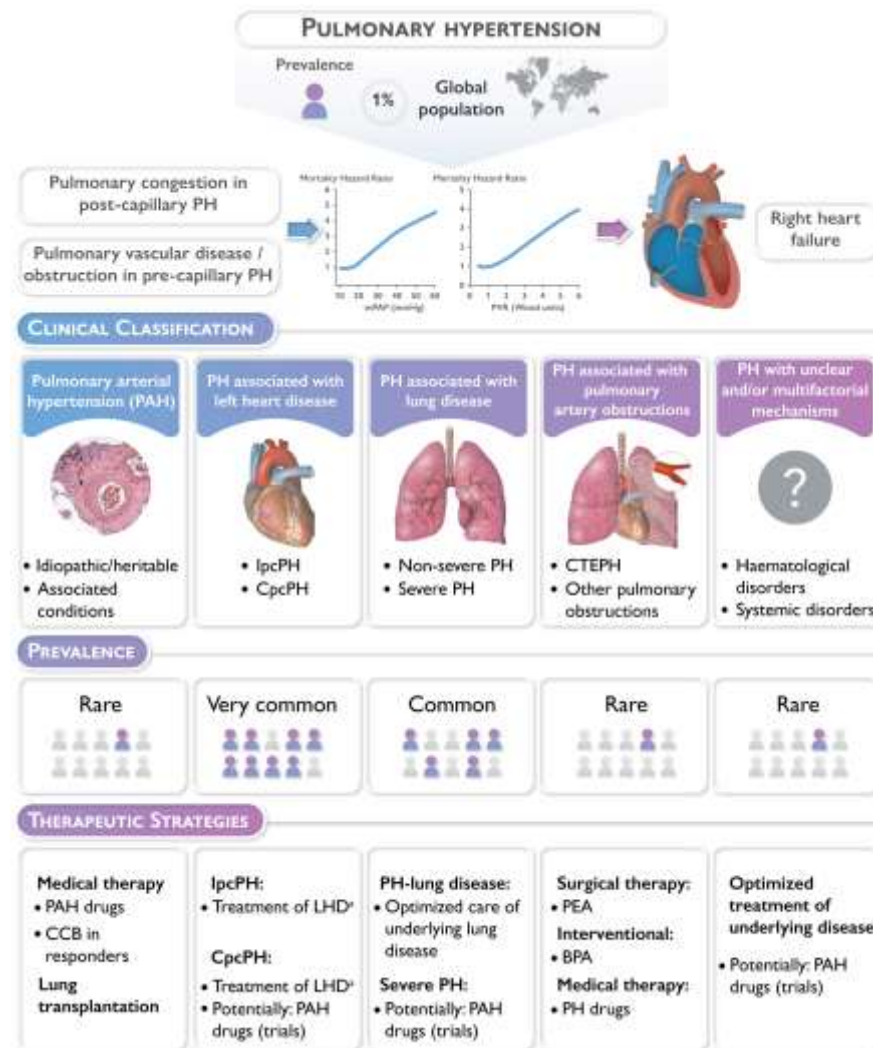


Figure 24-1: Classification, Epidemiology and management of Pulmonary Hypertension. Source: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH:

The diagnostic approach to PH is mainly focused on two tasks:

- The primary goal is to raise early suspicion of PH and ensure fast-track referral to PH centres in patients with a high likelihood of PAH, CTEPH, or other forms of severe PH.
- The second objective is to identify underlying diseases, especially LHD (group 2 PH) and lung disease (group 3 PH).

- **Clinical Presentation:**

Symptoms of PH are mainly linked to RV dysfunction, and typically associated with exercise in the earlier course of the disease.

The cardinal symptom is dyspnea on progressively minor exertion.

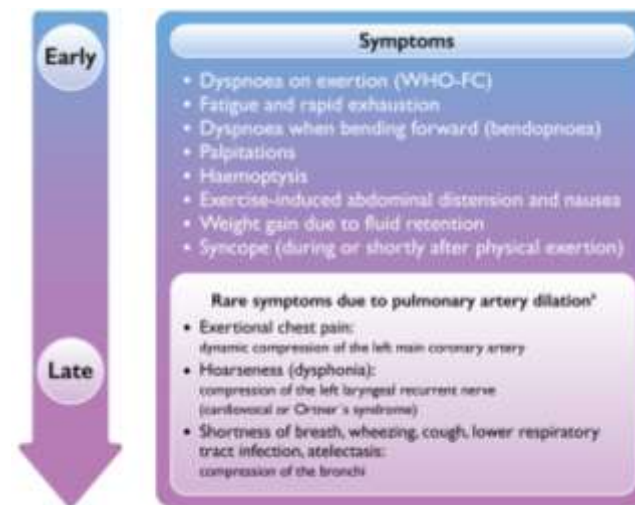


Figure 24-2: Symptoms in patients with pulmonary hypertension. (A) Thoracic compression syndromes are found in a minority of patients with PAH with pronounced dilation of the pulmonary artery, and may occur at any disease stage and even in patients with otherwise mild functional impairment. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

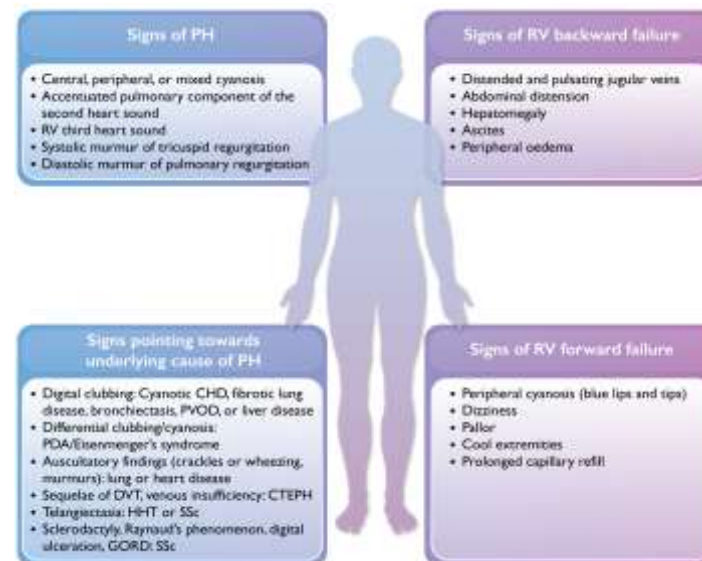


Figure 24-3: Clinical signs in patients with pulmonary hypertension. Source: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

N.B:

- Hypoxemia may be related to the cause of PH, such as pulmonary edema (left heart disease), lung disease, hypoventilation syndrome, or Eisenmenger syndrome and right-to-left shunting. On the other hand, PAH may, by itself, lead to hypoxemia, mainly in patients with patent foramen ovale. In those patients, the increased RA pressure “opens” the PFO, leading to a secondary right-to-left shunt (this shunt is the result rather than the cause of PAH).
- While hypoxemia may be seen in any PH, cyanosis at rest or with exercise characterizes Eisenmenger syndrome more than other causes of PH. Exercise-induced cyanosis or marked drop in O₂ desaturation is characteristic of an intracardiac shunt, wherein further right-to-left shunting occurs during exercise, as venous return increases.
- **ECG:** ECG abnormalities may raise suspicion of PH, deliver prognostic information, and detect arrhythmias and signs of LHD. A normal ECG does not exclude the presence of PH.

Typical ECG abnormalities in PH:

- P pulmonale (> 0.25 mV in lead II).
- Right axis deviation (QRS axis > 90°): In adults with clinical suspicion of PH (e.g. unexplained dyspnea on exertion), right axis deviation has a high predictive value for PH.
- RV hypertrophy (R/S > 1, with R > 0.5 mV in V₁; R in V₁ + S in lead V₅ > 1 mV).
- RBBB: complete or incomplete (qR or rSR patterns in V₁).
- RV strain pattern in advanced PH (ST depression/T-wave inversion in the right pre-cordial V₁₋₄ and inferior II, III, aVF leads).
- Prolonged QTc (unspecific): may reflect RV dysfunction and delayed myocardial repolarization, and is an independent predictor of mortality.
- **Echocardiography:** Echocardiography provides comprehensive information on right and left heart morphology, function, and valvular abnormalities, and gives estimates of hemodynamic parameters. It is also a valuable tool to detect the cause of PH, particularly LHD or congenital heart disease (CHD).

Given the heterogeneous nature of PH and the peculiar geometry of the RV, there is no single echocardiographic parameter that reliably informs about PH status and underlying aetiology. Therefore, a comprehensive echocardiographic evaluation for

suspected PH includes estimating the systolic pulmonary arterial pressure (sPAP) and detecting additional signs suggestive of PH, aiming at assigning an echocardiographic level of probability of PH. When interpreted in a clinical context, this probability can be used to decide the need for further investigation, including cardiac catheterization.

Table 24-3: Additional echocardiographic signs suggestive of pulmonary hypertension:

| (A) The ventricle | (B) Pulmonary Artery | (C) Inferior Vena Cava (IVC) |
|---|--|--|
| <ul style="list-style-type: none"> ○ <i>RV/LV basal diameter/area > 1.0</i> ○ <i>Flattening of the interventricular septum (LVEI > 1.1 in systole and/or diastole)</i> ○ <i>TAPSE/sPAP ratio < 0.55 mm/mmHg</i> | <ul style="list-style-type: none"> ○ <i>RVOT AT < 105 ms and/or mid-systolic notching</i> ○ <i>Early diastolic PR velocity > 2.2 m/s</i> ○ <i>PA diameter > AR diameter</i> ○ <i>PA diameter > 25 mm</i> | <ul style="list-style-type: none"> ○ <i>IVC diameter > 21 mm with decreased inspiratory collapse (< 50% with sniff or < 20% with quiet inspiration)</i> ○ <i>RA area (end-systole) > 18 cm²</i> |

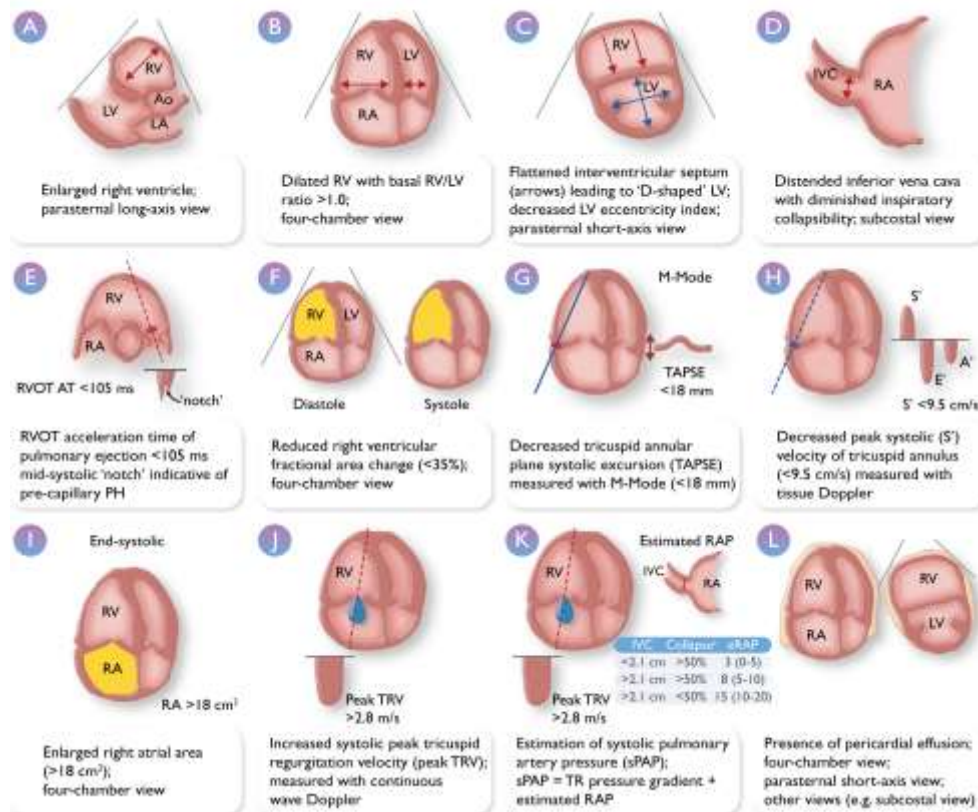


Figure 24-4: Transthoracic echocardiographic parameters in the assessment of pulmonary hypertension. (A) Refers to collapse on inspiration. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

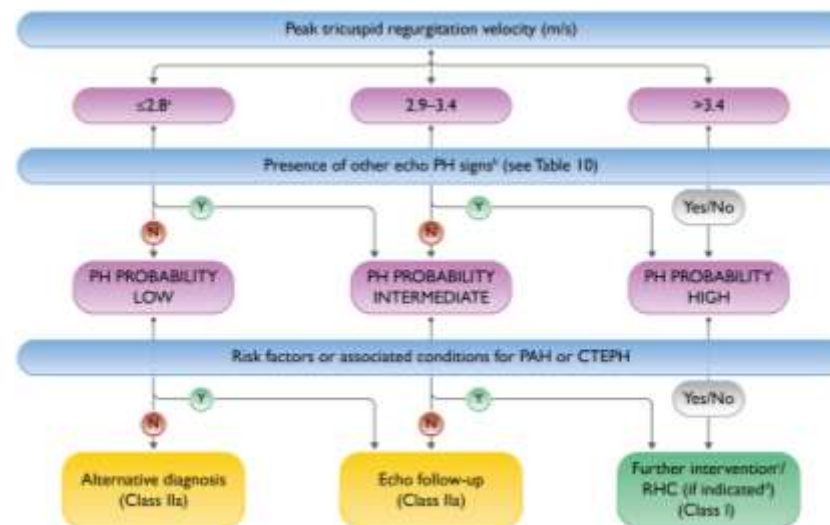


Figure 24-5: Echocardiographic probability of pulmonary hypertension and recommendations for further assessment. (A) Or unmeasurable. The TRV threshold of 2.8 m/s was not changed according to the updated haemodynamic definition of PH. (B) Signs from at least two categories (A/B/C) must be present to alter the level of echocardiographic probability of PH. (C) Further testing may be necessary (e.g., imaging, CPET). (D) RHC should be performed if useful information/a therapeutic consequence is anticipated (e.g., suspected PAH or CTEPH), and may not be indicated in patients without risk factors or associated conditions for PAH or CTEPH (e.g., when mild PH and predominant LHD or lung disease are present). **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

- **Other Imaging modalities:**

- **Ventilation/perfusion lung scan (V/Q scan):** V/Q SPECT is recommended in the diagnostic work-up of patients with suspected or newly diagnosed PH, to rule out or detect signs of CTEPH. The V/Q SPECT is superior to planar imaging and is the methodology of choice. In the absence of parenchymal lung disease, a normal perfusion scan excludes CTEPH with a negative predicted value of 98%.
- **Chest CT (with or without contrast):**

- In suspected/confirmed PH: a combination of three parameters (PA diameter ≥ 30 mm, RVOT wall thickness ≥ 6 mm, and septal deviation $\geq 140^\circ$ [or RV:LV ratio ≥ 1]) is highly predictive of PH.
- Non-contrast chest CT can determine the cause of PH (e.g, features of parenchymal lung disease).
- CT pulmonary angiography (CTPA) is mainly used to detect direct or indirect signs of CTEPH (sensitivity and specificity are 76% and 96%, respectively).
- **Cardiac MRI** accurately and reproducibly assesses atrial and ventricular size, morphology, and function.
- **Abdominal ultrasound:** should be part of the comprehensive diagnostic work-up of patients with newly diagnosed PH. A major objective is to search for liver disease and/or portal hypertension, or portocaval shunt (*Abernethy malformation*).
- **Blood tests and immunology:**
to identify comorbidities and possible causes or complications of PH. Laboratory tests include: blood counts; serum electrolytes; kidney function; uric acid; liver parameters; iron status; hepatitis viruses and HIV; BNP or NT-proBNP; and basic immunology laboratory work-up (anti-nuclear antibodies, anti-centromere antibodies, and anti-Ro).
Screening for biological markers of antiphospholipid syndrome is recommended in patients with CTEPH.
- **Cardiopulmonary exercise testing (CPET)** is a useful tool to assess the underlying pathophysiologic mechanisms leading to exercise intolerance. Patients with PAH show a typical pattern, with a low end-tidal partial pressure of carbon dioxide (PETCO₂), high ventilator equivalent for carbon dioxide (VE/VCO₂), low oxygen pulse (VO₂/HR), and low peak oxygen uptake (VO₂).
In populations at risk of PAH, such as those with SSc, a normal peak VO₂ excludes the diagnosis of PAH.
- **Right heart catheterization (RHC):**
 - RHC is the gold standard for diagnosing and classifying PH. The echocardiographic diagnosis of PH is falsely positive in up to 50% of patients, and, overall, the PA pressure value differs from the catheterization value by > 10 mmHg in 50% of patients. Echocardiography may under- or overestimate PA pressure in various PH etiologies.
 - **Technical tips:**
 - In the supine position, the mid thoracic level is recommended as the zero-reference level, which is at the level of the LA in most patients.

- Assess PCWP to determine if PH is secondary to left HF. The assessment of PCWP may be difficult in patients with severe PH:
 - (i) Segmental PA branches are dilated, which makes them difficult to wedge; thus, a hybrid PCWP-PA pressure tracing may be obtained and lead to overestimation of the true PCWP.
 - (ii) On the other hand, the true PCWP waveform may be flattened without distinct waves, as the retrograde transmission of LA pressure through the constricted pulmonary vasculature is damped.
- In the absence of an appropriate PCWP tracing, LVEDP needs to be measured.
- **Complications:** When performed in PH centres, the frequencies of serious adverse events (1.1%) and procedure-related mortality (0.05%) are low. Wedging a PA catheter in a patient with PH is associated with an increased risk of PA rupture; the most feared complication of RHC.
- **Contraindications:** A known thrombus or tumor in the RV or RA, recently implanted (< 1 month) pacemaker, mechanical right heart valve, TriClip, and acute infection are contraindications to RHC.

| Table 24-4: Hemodynamic measures obtained during right heart catheterization: | |
|---|--------------|
| Measured variables | Normal value |
| RA pressure | 2-6 mmHg |
| Systolic PA pressure | 15-30 mmHg |
| Diastolic PA pressure | 4-12 mmHg |
| Mean PA pressure | 8-20 mmHg |
| Pulmonary arterial wedge pressure (PAWP) | ≤ 15 mmHg |
| Cardiac output | 4-8 L/min |
| Mixed venous oxygen saturation (SvO ₂) | 65-80% |
| Arterial oxygen saturation (SaO ₂) | 95-100% |
| Systemic blood pressure | 120/80 mmHg |

| Calculated parameters: | | |
|--|--------------------------------|------------------------------|
| Pulmonary vascular resistance (PVR) | PVR = [mPAP–PAWP] / CO | 0.3-2.0 WU |
| Pulmonary vascular resistance index (PVRI) | PVRI = [mPAP–PAWP] / CI | 3-3.5 WU.m ² |
| Total pulmonary resistance (TPR) | TRP = mPAP / CO | < 3 WU |
| Cardiac index (CI) | CI = CO / BSA | 2.5-4.0 L/min.m ² |
| Stroke volume (SV) | SV = CO / HR | 60-100 mL |
| Stroke volume index (SVI) | SVI = SV / BSA | 33-47 mL/m ² |
| Pulmonary arterial compliance (PAC) | PAC = SV / (sPAP–dPAP) | > 2.3 mL/mmHg |

○ **Vasoreactivity testing:**

- The purpose of vasoreactivity testing in PAH is to identify acute vasoresponders who may be candidates for treatment with high-dose CCBs. Only 10% of patients with PAH have a positive response to vasodilator challenge.
- Pulmonary vasoreactivity testing is only recommended in patients with IPAH, HPAH, or DPAH ⁽¹⁾.
- It can be done using inhaled nitric oxide (10-20 p.p.m.) **or** inhaled iloprost (5-10 µg).
- These agents are uptitrated until the max. dose is reached, **or** till systemic intolerance (dyspnea, nausea), **or** one of the 5 negative endpoints (hypotension, ↓ CO, ↑ PCWP, ↑ RA pressure, ↓ SaO₂).
- A positive acute response is defined as a reduction in mPAP by ≥ 10 mmHg to reach an absolute value ≤ 40 mmHg, with increased or unchanged CO.

(1) Vasoreactivity testing is useful in two more situations:

- Patients with left-to-right shunt (ASD, VSD, PDA) who have PH with a PVR > 2/3 SVR **or** > 6 WU need to have vasoreactivity testing before shunt correction to ensure that PH is reversible; otherwise shunt closure may precipitate right heart failure.
- Patients with advanced left HF who are considered for heart transplantation and have PH with high PVR require vasoreactivity testing to assess the reversibility of PH and their operability. Nitroprusside and milrinone are the vasodilators of choice, as they reduce PVR in reactive PH but also reduce LV afterload, which prevents the increase in PCWP. In this case, the use of prostanoids may increase PCWP and is poorly tolerated.

- Since non-responders still respond well to the chronic administration of potent pulmonary vasodilators (prostacyclin, bosentan, sildenafil), one may wonder what the rationale for vasodilator challenge is. The rationale for vasodilator challenge is threefold:
 - A. Positive responders to vasodilator challenge may respond to chronic CCBs therapy;
 - B. Positive responders have a better long-term prognosis;
 - C. The hemodynamic tolerance to vasodilator therapy is assessed. One should ensure that PCWP does not increase and cardiac output and systemic pressure do not decrease with vasodilators. In fact, a vasodilator challenge may be used as a form of left heart stress testing, unveiling occult left HF.
- **Exercise RHC:** The main reason to perform exercise RHC is to investigate patients with unexplained dyspnea and normal resting hemodynamics in order to detect early PVD or left heart dysfunction.
- **Fluid challenge:** Patients with normal LVEDP and PCWP may still have occult HF. If suspected clinically, give a volume load (500 mL of saline over 5-10 min) and see if PCWP or LVEDP increases, unveiling left HF as the cause of PH (suggestive of HFpEF).

| Table 24-5: ESC Recommendations for diagnostic evaluation of Pulmonary hypertension: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Echocardiography: | | |
| <i>Echocardiography is recommended as the first-line, non-invasive, diagnostic investigation in suspected PH.</i> | I | B |
| <i>It is recommended to assign an echocardiographic probability of PH, based on an abnormal TR velocity (TRV) and the presence of other echocardiographic signs suggestive of PH.</i> | I | B |
| <i>It is recommended to maintain the current threshold for TRV (> 2.8 m/s) for echocardiographic probability of PH according to the updated hemodynamic definition</i> | I | C |
| <i>Based on the probability of PH by echocardiography, further testing should be considered in the clinical context (i.e., symptoms and risk factors or associated conditions for PAH/CTEPH)</i> | IIa | B |
| <i>In symptomatic patients with intermediate echocardiographic probability of PH, CPET may be considered to further determine the likelihood of PH.</i> | IIb | C |

| | | |
|---|-----|---|
| Imaging and Laboratory workup: | | |
| <i>Routine biochemistry, hematology, immunology, HIV testing, and thyroid function tests are recommended in all patients with PAH, to identify associated conditions.</i> | I | C |
| <i>Abdominal ultrasound is recommended for the screening of portal hypertension.</i> | I | C |
| <i>Chest CT should be considered in all patients with PH.</i> | Ila | C |
| <i>Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to assess for CTEPH.</i> | I | C |
| <i>CT pulmonary angiography is recommended in the work-up of patients with suspected CTEPH.</i> | I | C |
| <i>Digital subtraction angiography should be considered in the work-up of patients with CTEPH.</i> | Ila | C |
| Other diagnostic tests: | | |
| <i>Pulmonary function tests with DLCO are recommended in the initial evaluation of patients with PH.</i> | I | C |
| <i>Open or thoracoscopic lung biopsy is not recommended in patients with PAH.</i> | III | C |
| Right heart catheterization: | | |
| <i>It is recommended that RHC is performed to confirm the diagnosis of PH (especially PAH or CTEPH) and to support treatment decisions.</i> | I | B |
| <i>In patients with suspected or known PH, it is recommended that RHC is performed in experienced centres.</i> | I | C |
| <i>It is recommended that RHC comprises a complete set of hemodynamics and is performed following standardized protocols.</i> | I | C |
| Vasoreactivity testing: | | |
| <i>Vasoreactivity testing is recommended in patients with I/H/DPAH to detect those who can be treated with high doses of a CCB.</i> | I | B |
| <i>It is recommended that vasoreactivity testing is performed at PH centres</i> | I | C |

| | | |
|---|------------|----------|
| <i>It is recommended to consider a positive response to vasoreactivity testing by a reduction in mPAP ≥ 10 mmHg to reach an absolute value of mPAP ≤ 40 mmHg with an increased or unchanged CO ⁽¹⁾</i> | I | C |
| <i>Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing</i> | I | C |
| <i>Vasoreactivity testing, for identifying candidates for CCB therapy, is not recommended in patients with PAH other than I/H/DPAH, and in PH groups 2, 3, 4, and 5</i> | III | C |

(1) Testing should also be performed in patients with a baseline mPAP ≤ 40 mmHg, in whom the same responder criteria apply.

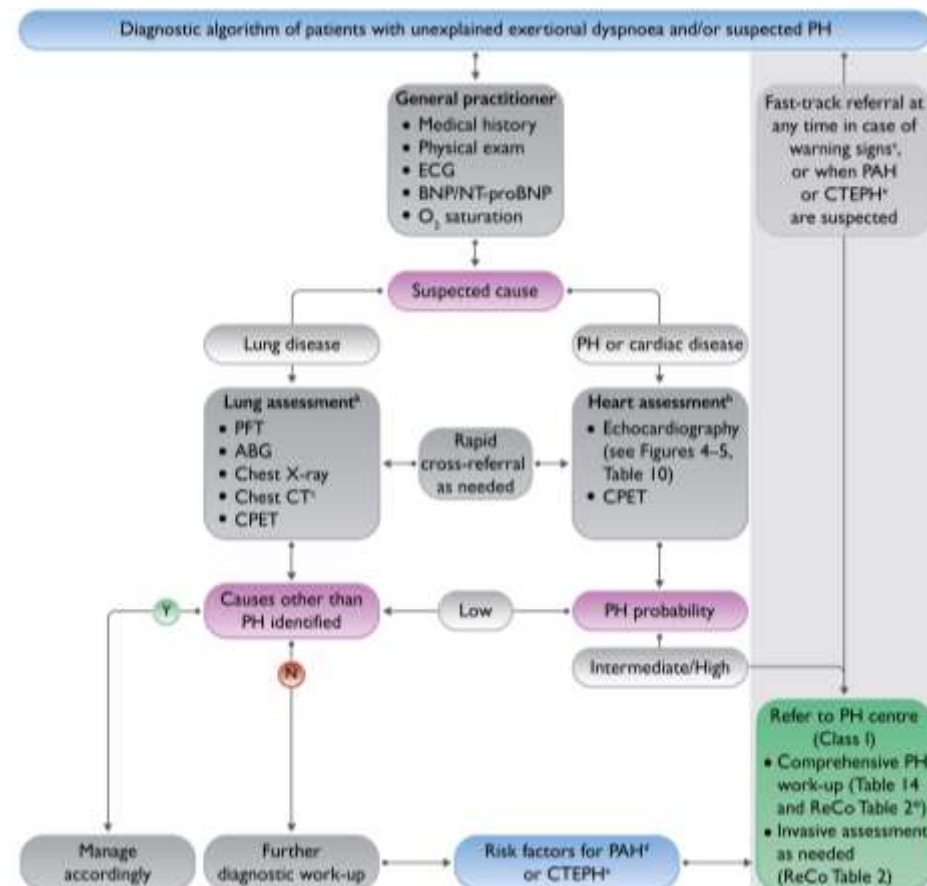


Figure 24-6: Diagnostic algorithm of patients with unexplained dyspnoea and/or suspected pulmonary hypertension. (A) Warning signs include rapid progression of symptoms, severely reduced exercise capacity, pre-syncope or syncope on mild exertion, signs of right heart failure. (B) Lung and heart assessment by specialist as per local practice. (C) As indicated; CT pulmonary angiography recommended if PH suspected. (D) Includes: connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. (E) History of PE, permanent intravascular devices, inflammatory bowel diseases, essential thrombocythaemia, splenectomy, high-dose thyroid hormone replacement, and malignancy. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Screening and Early detection:

Despite the advent of PAH therapies that prevent clinical worsening and effective interventions for CTEPH, the time from symptom onset to PH diagnosis remains at > 2 years, with most patients presenting with advanced disease. Decreasing the time to diagnosis may enable treatment at an earlier stage when therapies may be more effective.

| Table 24-6: ESC Recommendations for screening and improved detection of PAH and CTEPH: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Systemic sclerosis: | | |
| <i>In patients with SSc, an annual evaluation of the risk of having PAH is recommended</i> | I | B |
| <i>In adult patients with SSc with > 3 years' disease duration, an FVC \geq 40%, and a DLCO < 60%, the DETECT algorithm ⁽¹⁾ is recommended to identify asymptomatic patients with PAH.</i> | I | B |
| <i>In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH.</i> | I | C |
| <i>Assessing the risk of having PAH based on an evaluation of breathlessness, in combination with echocardiogram or PFTs and BNP/NT-proBNP, should be considered in patients with SSc</i> | IIa | B |
| <i>Policies to evaluate the risk of having PAH should be considered in hospitals managing patients with SSc</i> | IIa | C |

(1) The DETECT algorithm is a tool to identify PAH in patients with systemic sclerosis in the asymptomatic stages. It has 2-steps:

- **Step 1** (Non echocardiographic variables): to detect people who should be referred to perform echocardiography.
Components: - FVC% predicted/DLCO% predicted. - Current/past telangiectasia. - Serum anticentromere antibodies.
- Serum NT-proBNP - Serum urate. - Right-axis deviation on ECG
- **Step 2** (Echocardiographic variables): to detect people who should be referred to perform RHC.
Components: RA area, TR velocity.

| | | |
|--|------------|----------|
| <i>In symptomatic patients with SSc, exercise echocardiography or CPET, or CMR may be considered to aid decisions to perform RHC.</i> | IIb | C |
| <i>In patients with CTD with overlap features of SSc, an annual evaluation of the risk of PAH may be considered.</i> | IIb | C |
| CTEPH/CTEPD: | | |
| <i>In patients with persistent or new-onset dyspnea or exercise limitation following PE, further diagnostic evaluation to assess for CTEPH/CTEPD is recommended.</i> | I | C |
| <i>For symptomatic patients with mismatched perfusion lung defects beyond 3 months of anticoagulation for acute PE, referral to a PH/CTEPH centre is recommended after considering the results of echocardiography, BNP/ NT-proBNP, and/or CPET.</i> | I | C |
| Other: | | |
| <i>Counselling regarding the risk of PAH and annual screening are recommended in individuals who test positive for PAH-causing mutations ⁽¹⁾ and in first-degree relatives of patients with HPAH.</i> | I | B |
| <i>In patients referred for liver transplantation, echocardiography is recommended as a screening test for PH</i> | I | C |
| <i>Further tests (echocardiography, BNP/NT-proBNP, PFTs, and/or CPET) should be considered in symptomatic patients with CTD, portal hypertension, or HIV to screen for PAH.</i> | IIa | B |

(1) Mutations in the gene encoding BMPRII-a receptor for the TGF- β (transforming growth factor-beta) account for over 70% of families with PAH and \approx 20% of sporadic cases.

Pulmonary arterial hypertension (Group 1)

▪ Severity and risk assessment:

At diagnosis and during follow-up, the WHO-FC is one of the strongest predictors of survival and disease progression.

Table 24-7: WHO classification of functional status of patients with pulmonary hypertension ⁽¹⁾:

| Class | Description |
|-------------------|--|
| WHO-FC I | <i>Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope</i> |
| WHO-FC II | <i>Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</i> |
| WHO-FC III | <i>Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope</i> |
| WHO-FC IV | <i>These patients manifest signs of right HF. Dyspnea and/or fatigue may even be present at rest.</i> |

• **Risk stratification at diagnosis:**

For risk stratification at diagnosis, use of the **three-strata model** is recommended.

Table 24-8: Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model):

| | Low risk (< 5%) ⁽²⁾ | Intermediate (5-20%) | High risk (> 20%) |
|--------------------------------|--------------------------------|-----------------------------------|---------------------------------|
| Signs of right HF | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncope ⁽³⁾ | Repeated syncope ⁽⁴⁾ |
| WHO-FC | I, II | III | IV |

⁽¹⁾ Functional classification of PH modified after the NYHA functional classification according to the WHO 1998.

⁽²⁾ Estimated 1-year mortality.

⁽³⁾ Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.

⁽⁴⁾ Repeated episodes of syncope even with little or regular physical activity.

| | | | |
|-----------------------------|--|---|--|
| 6MWD ⁽¹⁾ | > 440 m | 165-440 m | < 165 m |
| CPET | - $\text{VO}_{2\text{max}} > 15 \text{ mL/min/kg}$ (> 65% pred.) - $\text{VE/VCO}_2 \text{ slope}^{(2)} < 36$ | - $\text{VO}_{2\text{max}} 11\text{--}15 \text{ mL/min/kg}$ (35-65% pred.) - $\text{VE/VCO}_2 \text{ slope } 36\text{--}44$ | - $\text{VO}_{2\text{max}} < 11 \text{ mL/min/kg}$ (< 35% pred.) - $\text{VE/VCO}_2 \text{ slope } > 44$ |
| BNP or NT-proBNP | - < 50 ng/L - < 300 ng/L | - 50-800 ng/L - 300-1100 ng/L | - > 800 ng/L - > 1100 ng/L |
| Echocardiography | - RA area < 18 cm^2 - $\text{TAPSE/sPAP} > 0.32$ - No pericardial effusion | - RA area $18\text{--}26 \text{ cm}^2$ - $\text{TAPSE/sPAP } 0.19\text{--}0.32$ - Minimal pericardial effusion | - RA area > 26 cm^2 - $\text{TAPSE/sPAP} < 0.19$ - Moderate or large pericardial effusion |
| Cardiac MRI | - $\text{RVEF} > 54\%$ - $\text{SVI} > 40 \text{ mL/m}^2$ - $\text{RVESVI} < 42 \text{ mL/m}^2$ | - $\text{RVEF } 37\text{--}54\%$ - $\text{SVI } 26\text{--}40 \text{ mL/m}^2$ - $\text{RVESVI } 42\text{--}54 \text{ mL/m}^2$ | - $\text{RVEF} < 37\%$ - $\text{SVI} < 26 \text{ mL/m}^2$ - $\text{RVESVI} > 54 \text{ mL/m}^2$ |
| Haemodynamics | - $\text{RAP} < 8 \text{ mmHg}$ - $\text{CI} \geq 2.5 \text{ L/min/m}^2$ - $\text{SVI} > 38 \text{ mL/m}^2$ - $\text{SvO}_2 > 65\%$ | - $\text{RAP } 8\text{--}14 \text{ mmHg}$ - $\text{CI } 2.0\text{--}2.4 \text{ L/min/m}^2$ - $\text{SVI } 31\text{--}38 \text{ mL/m}^2$ - $\text{SvO}_2 60\text{--}65\%$ | - $\text{RAP} > 14 \text{ mmHg}$ - $\text{CI} < 2.0 \text{ L/min/m}^2$ - $\text{SVI} < 31 \text{ mL/m}^2$ - $\text{SvO}_2 < 60\%$ |

- **Follow-up visits:**

(1) Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

(2) The minute ventilation/carbon dioxide production (VE/VCO_2) slope reflects the increase in ventilation in response to CO_2 production, and thus shows increased ventilatory drive. A normal ventilatory response of the VE/VCO_2 slope should be under 30.0. Patients with cardiopulmonary disease often present an abnormal ventilation response, characterized by an increase in the VE/VCO_2 slope; for any given VCO_2 level, VE is greater than normal.

- The optimal timing of follow-up has not been determined, but may be every 3-6 months in stable patients ⁽¹⁾ and in case of any clinical deterioration.
- At each visit, the assessment should include: clinical assessment (including WHO-FC), ECG, pulse oximetry, 6MWT, Blood tests (including NT-proBNP), and echocardiography.
- At follow-up, the **four-strata model** is recommended as a basic risk-stratification tool, but additional variables should be considered as needed, particularly right heart imaging and hemodynamics ⁽²⁾. Patient's factors such as age, sex, disease type, comorbidities, and kidney function should be considered as well.

| Table 24-9: Variables used to calculate the simplified four-strata risk-assessment tool | | | | |
|---|--------------|-----------------------|------------------------|-----------------|
| | Low risk | Intermediate-low risk | Intermediate-high risk | High risk |
| Points assigned | 1 | 2 | 3 | 4 |
| WHO-FC | I or II | - | III | IV |
| 6MWD, m | > 440 | 320–440 | 165–319 | < 165 |
| BNP or NT-proBNP, ng/L | < 50 <300 | 50–199 300–649 | 200–800 650–1100 | > 800 > 1100 |
| Risk is calculated by dividing the sum of all points by the number of variables and rounding to the next integer. | | | | |

| Table 24-10: ESC Recommendations for evaluating the disease severity and risk of death in patients with pulmonary arterial hypertension: | | |
|--|-------|-------|
| Recommendations | Class | Level |

- (1) Intervals to be adjusted according to patient needs, PAH aetiology, risk category, demographics, and comorbidities.
- (2) Some centres perform invasive follow-up assessment regularly while others do them as clinically indicated. There is no evidence that either strategy is associated with better outcomes. Generally, RHC is recommended at baseline and should be considered at 3-6 months after changes in therapy or in case of clinical worsening.

| | | |
|---|------------|----------|
| <i>It is recommended to evaluate disease severity in patients with PAH with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiography, and hemodynamic evaluations.</i> | I | B |
| <i>Achieving and maintaining a low-risk profile on optimized medical therapy is recommended as a treatment goal in patients with PAH.</i> | I | B |
| <i>For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data, including hemodynamics</i> | I | B |
| <i>For risk stratification during follow-up, the use of a four-strata model (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary.</i> | I | B |
| <i>In some PAH aetiologies and patients with comorbidities, optimization of therapy should be considered on an individual basis, while acknowledging that a low-risk profile is not always achievable.</i> | Ila | B |

▪ **Treatment:**

Managing patients with PAH requires a comprehensive treatment strategy and multidisciplinary care including general measures, PAH drugs and lung transplant in particular cases. Also, the systemic consequences of PH and right-sided HF should be appropriately managed.

• **General recommendations:**

| Table 24-11: ESC Recommendations for general measures and special circumstances: | | |
|---|--------------|--------------|
| <i>Recommendation</i> | <i>Class</i> | <i>Level</i> |
| General measures: | | |

| | | |
|---|------------|----------|
| <i>Supervised exercise training is recommended in patients with PAH under medical therapy.</i> | I | A |
| <i>In patients with PAH, the following is recommended:</i> <ul style="list-style-type: none"> <i>- Psychosocial support.</i> <i>- Immunization against SARS-CoV-2, influenza, and Streptococcus pneumoniae</i> <i>- Diuretics if there is signs of RV failure and fluid retention</i> <i>- Long-term oxygen therapy if PaO₂ is < 60 mmHg (8 kPa) on at least two occasions.</i> <i>- Correction of iron status in the presence of iron-deficiency anemia.</i> | I | C |
| <i>In the absence of anemia, iron repletion may be considered in patients with PAH with iron deficiency.</i> | IIb | C |
| <i>Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis</i> | IIb | C |
| <i>The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (i.e. high blood pressure, coronary artery disease, left HF, or arrhythmias)</i> | III | C |
| Women of childbearing potential: | | |
| <i>It is recommended that women of childbearing potential with PAH are counselled at the time of diagnosis about the risks and uncertainties associated with becoming pregnant; this should include advice against becoming pregnant, and referral for psychological support if needed</i> | I | C |
| <i>It is recommended to provide women of childbearing potential with PAH with clear contraceptive advice, considering the individual needs of the woman but recognizing that the implications of contraceptive failure are significant in PAH</i> | I | C |
| <i>It is recommended that women with PAH who consider pregnancy or who become pregnant receive prompt counselling in an experienced PH centre, to facilitate genetic counselling and shared decision-making, and to provide psychological support to the patients and their families where needed.</i> | I | C |

| | | |
|--|------------|----------|
| <i>For women with PAH having a termination of pregnancy, it is recommended to be performed in PH centres, with psychological support provided to the patients and their families</i> | I | C |
| <i>For women with PAH who desire to have children, where available, adoption and surrogacy with pre conception genetic counselling may be considered</i> | IIb | C |
| <i>As teratogenic potential has been reported in pre-clinical models for endothelin receptor antagonists and riociguat, these drugs are not recommended during pregnancy.</i> | III | B |
| Special Circumstances: | | |
| <i>In-flight, oxygen administration is recommended for patients using oxygen or whose PaO₂ is < 60 mmHg (8 kPa) at sea level.</i> | I | C |
| <i>For interventions requiring anaesthesia, multidisciplinary consultation at a PH centre to assess risk and benefit should be considered</i> | IIa | C |

- **Pharmacological treatment:**

Patients who acutely respond to vasoreactivity testing should be treated with CCBs (associated with a dramatic improvement in survival).

Non-responders to vasoreactivity testing are treated through one of the three classic pathways of targeted therapy for PAH:

- **Endothelin 1 pathway:** Endothelin-1 receptor antagonists (ERA): bosentan, ambrisentan, macitentan.
- **Prostacyclin (PGI₂) pathway:**
 - Prostacyclin (PGI₂) analogues: e.g., Epoprostenol and Treprostinil, and Iloprost.
 - PGI₂ receptor (IP) agonists: e.g., selexipag.
- **Nitric oxide pathway:**
 - Phosphodiesterase-5 inhibitors: e.g., Sildenafil and Tadalafil.
 - Stimulator of guanylate cyclase: e.g., Riociguat.

N.B:

- PAH therapies improve PVR, RV function and size on echo, RA pressure, and cardiac output *without much of an effect on PA pressure*. Along with the reduction in PVR, cardiac output increases, which may mask any PA pressure improvement (PA pressure ~ PVR × cardiac output).
- Nitrates increase cGMP in the systemic but not pulmonary arteries and are not effective in PAH.

| Table 24-12: Dosing of pulmonary arterial hypertension medication in adults: | | |
|--|-----------------------------|--------------------------|
| | Starting dose | Target dose |
| Calcium channel blockers: | | |
| Amlodipine | 5 mg o.d. | 15-30 mg o.d. |
| Felodipine | 5 mg o.d. | 15-30 mg o.d. |
| Diltiazem | 60 mg b.i.d. | 120-360 mg b.i.d. |
| Nifedipine | 10 mg t.i.d. | 20-60 mg b.i.d. or t.i.d |
| Endothelin receptor antagonists (oral administration): | | |
| Ambrisentan | 5 mg o.d | 10 mg o.d. |
| Bosentan | 62.5 mg b.i.d | 125 mg b.i.d. |
| Macitentan | 10 mg o.d. | |
| Phosphodiesterase 5 inhibitors (oral administration): | | |
| Sildenafil | 20 mg t.i.d. ⁽¹⁾ | |
| Tadalafil | 20 mg o.d | 40 mg o.d. |
| Prostacyclin analogues (oral administration): | | |
| Beraprost sodium | 20 µg t.i.d. | 40 µg t.i.d. |
| Beraprost extended release | 60 µg b.i.d. | 180 µg b.i.d. |

(1) Sildenafil is approved at a dose of 20 mg t.i.d. but doses used in practice vary widely and are sometimes higher.

| | | |
|--|-----------------------------------|--|
| Treprostinil | 0.25 mg b.i.d. or 0.125 mg t.i.d. | Maximum tolerated dose |
| Prostacyclin receptor agonist (oral administration): | | |
| Selexipag | 200 µg b.i.d. | 1600 µg b.i.d. |
| Soluble guanylate cyclase stimulator (oral administration): | | |
| Riociguat ⁽¹⁾ | 1 mg t.i.d. | 2.5 mg t.i.d. |
| Prostacyclin analogues (inhaled administration): | | |
| Iloprost | 2.5 µg 6-9 times per day | 5.0 µg 6-9 times per day |
| Treprostinil | 18 µg 4 times per day | 54-72 µg 4 times per day |
| Prostacyclin analogues (i.v. or s.c. administration): | | |
| Epoprostenol i.v. | 2 ng/kg/min | Determined by tolerability and effectiveness, with wide individual variability. Typical dose range at 1 year is: For Epoprostenol= 16-30 ng/kg/min, For Treprostinil= 25-60 ng/kg/min |
| Treprostinil s.c. or i.v. | 1.25 ng/kg/min | |

(1) In patients at risk of systemic hypotension, riociguat may be started at 0.5 mg t.i.d.

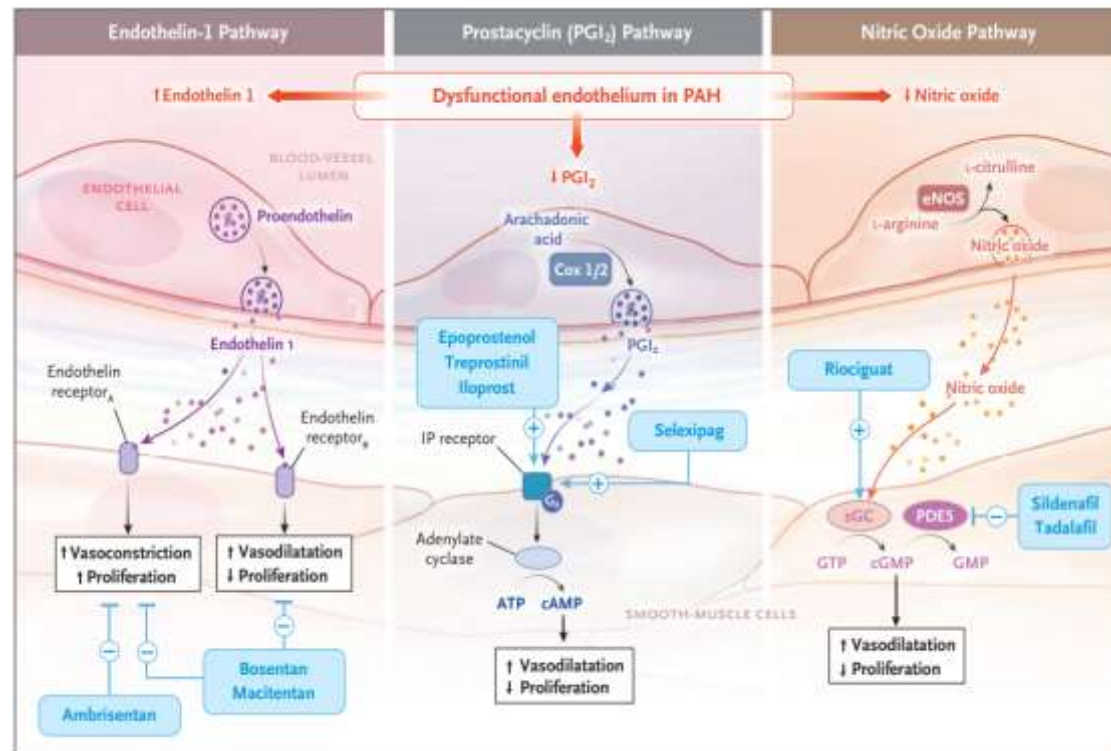


Figure 24-7: Three Classic Pathways of Targeted Therapy for PAH. Current targeted therapy is aimed at correcting endothelial dysfunction by inhibiting the endothelin pathway and enhancing the prostacyclin (PGI₂) and NO pathways. Endothelin 1 (ET1), which is increased in PAH, can bind to either the endothelin A (ETA) receptor, causing vasoconstriction (of smooth muscle cells) and cell proliferation, or the endothelin B (ETB) receptor, causing vasodilation and antiproliferation. The expression and function of the PGI₂ and NO pathways are decreased in PAH, resulting, respectively, in diminished cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are second messengers responsible for vasodilation and antiproliferation. Agents that increase cAMP include PGI₂ analogues given intravenously (e.g., epoprostenol and treprostinil), subcutaneously (e.g., treprostinil), by inhalation (e.g., iloprost and treprostinil), orally (treprostinil), or with the use of oral PGI₂ receptor (IP) agonists (e.g., selexipag). Increased cGMP release can be achieved with inhaled NO (used essentially in the catheterization laboratory or intensive care unit), which stimulates soluble guanylate cyclase (sGC), or by inhibiting phosphodiesterase type 5 (PDE5, which degrades cGMP into GMP) with the use of oral PDE5 inhibitors (sildenafil or tadalafil). Direct sGC stimulators (e.g., oral riociguat) can increase the release of cGMP independently of NO release. **Source:** Hassoun PM. Pulmonary Arterial Hypertension. *N Engl J Med.* 2021 Dec 16;385(25):2361-2376. doi: 10.1056/NEJMra2000348. PMID: 34910865.

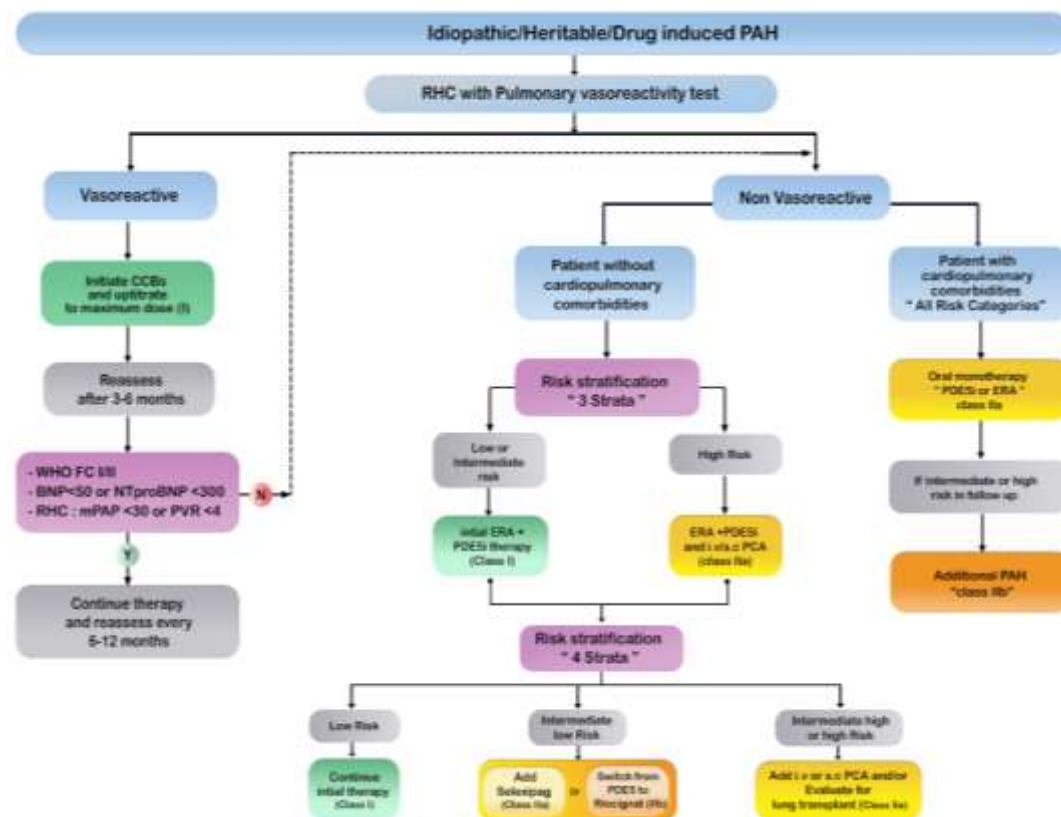


Figure 24-8: Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated PAH. Vasoreactive response is defined as a reduction in mPAP by ≥ 10 mmHg to reach an absolute value ≤ 40 mmHg, with increased or unchanged CO. **Cardiopulmonary comorbidities** are conditions associated with an increased risk of LV diastolic dysfunction, and include obesity, hypertension, DM, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO ($< 45\%$ of the predicted value). **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Table 24-13: ESC Recommendations for the treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension:

| Recommendation | Class | Level |
|---|--------------|--------------|
| <i>High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing.</i> | I | C |
| <i>Close follow-up with complete reassessment after 3-4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs.</i> | I | C |
| <i>Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked hemodynamic improvement (mPAP < 30 mmHg and PVR < 4 WU)</i> | I | C |
| <i>Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked hemodynamic improvement after high doses of CCBs.</i> | I | C |
| <i>In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered</i> | IIa | C |
| <i>CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (e.g. Raynaud's phenomenon)</i> | III | C |

Table 24-14: ESC Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated PAH:

| Recommendation | Class | Level |
|---|--------------|--------------|
| Without cardiopulmonary comorbidities: | | |

| | | |
|---|------------|----------|
| <i>In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended.</i> | I | B |
| <i>In patients with IPAH/HPAH/DPAH who present at high risk of death, initial triple combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered ⁽¹⁾.</i> | IIa | C |
| <i>In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, the addition of selexipag should be considered.</i> | IIa | B |
| <i>In patients with IPAH/HPAH/DPAH who present at intermediate-high or high risk of death while receiving ERA/PDE5i therapy, the addition of i.v./s.c. prostacyclin analogues and referral for LTx evaluation should be considered.</i> | IIa | C |
| <i>In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered.</i> | IIb | B |
| With cardiopulmonary comorbidities: | | |
| <i>In patients with IPAH/HPAH/DPAH and cardiopulmonary comorbidities, initial monotherapy with a PDE5i or an ERA should be considered.</i> | IIa | C |
| <i>In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medication may be considered on an individual basis.</i> | IIb | C |

Table 24-15: ESC Recommendations for initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities:

Recommendation

Class Level

(1) Initial triple-combination therapy including i.v./s.c. prostacyclin analogues may also be considered in patients at intermediate risk but severe haemodynamic impairment (e.g. RAP \geq 20 mmHg, CI $<$ 2.0 L/min/m², SVI $<$ 31 mL/m², and/or PVR \geq 12 WU).

| | | |
|--|------------|----------|
| <i>Initial combination therapy with ambrisentan or macitentan and tadalafil is recommended.</i> | I | B |
| <i>Initial combination therapy with other ERAs and PDE5is should be considered</i> | IIa | B |
| <i>Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended</i> | III | B |

Table 24-16: ESC Recommendations for sequential drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension:

| Recommendation | Class | Level |
|--|--------------|--------------|
| General recommendation: | | |
| <i>It is recommended to base treatment escalations on risk assessment and general treatment strategies</i> | I | C |
| Evidence from studies with a composite morbidity/mortality endpoint as the primary outcome measure: | | |
| To reduce the risk of morbidity/mortality events: | | |
| - Addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended | I | B |
| - The addition of selexipag to ERA _{sc} and/or PDE5is is recommended. | I | B |
| - The addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended. | I | B |
| - The addition of bosentan to sildenafil is not recommended | III | B |
| Evidence from studies with change in 6MWD as the primary outcome measure: | | |
| To improve exercise capacity: | | |
| - The addition of sildenafil to epoprostenol is recommended. | I | B |
| - The addition of inhaled treprostinil to sildenafil or bosentan monotherapy should be considered. | IIa | B |
| - The addition of riociguat to bosentan should be considered. | IIa | B |
| | IIb | C |

| | | |
|--|-----|---|
| - The addition of tadalafil to bosentan may be considered. | IIb | B |
| - The addition of inhaled iloprost to bosentan may be considered. | IIb | C |
| - The addition of ambrisentan to sildenafil may be considered. | IIb | C |
| - The addition of bosentan to sildenafil may be considered. | IIb | C |
| - The addition of sildenafil to bosentan may be considered. | IIb | C |
| - Other sequential double- or triple-combination therapies may be considered to improve exercise capacity and/or alleviate PH symptoms | IIb | C |
| Evidence from studies with safety of combination therapy as the primary outcome measure: | | |
| Combining riociguat and PDE5is is not recommended ⁽¹⁾ | III | B |

- **Lung transplant in patients with PAH:**

- **Criteria for Referral:**

- Potentially eligible patients for whom LTx might be an option in case of treatment failure.
- ESC/ERS intermediate-high **or** high risk **or** REVEAL risk score > 7 ⁽²⁾ on appropriate PAH medication.
- Progressive disease or recent hospitalization for worsening PAH.
- Need for i.v. or s.c. prostacyclin therapy.
- Known or suspected high-risk variants, such as pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH), systemic sclerosis, or large and progressive pulmonary artery aneurysms.
- Signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications, such as recurrent haemoptysis.

(1) As they both act on the cGMP system (risk of hypotension without much benefit). The PATENT plus study investigated the safety and efficacy of the combination of sildenafil and riociguat; however, combining riociguat with any PDE5i is contraindicated.

(2) The Registry to Evaluate Early and Longterm PAH Disease Management (REVEAL) risk score, developed for risk assessment in patients with PAH. Based on 1-year survival, a patient's risk was categorized as low (1-7), average (8), moderately high (9), high (10-11), or very high (≥ 12).

○ **Criteria for Listing:**

- Patient has been fully evaluated and prepared for transplantation.
- ESC/ERS high risk **or** REVEAL risk score > 10 on appropriate PAH medication, usually including i.v. or s.c. prostacyclin analogues.
- Progressive hypoxaemia, especially in patients with PVOD or PCH.
- Progressive, but not end-stage liver or kidney dysfunction due to PAH, or life-threatening haemoptysis.

| Table 24-17: ESC Recommendations for Mechanical circulatory support and lung transplantation: | | |
|---|--------------|--------------|
| Recommendation | Class | Level |
| Mechanical circulatory support: | | |
| <i>Mechanical circulatory support may be an option for selected patients as a bridge to transplantation or recovery, and interhospital transfer should be considered if such resources are unavailable on site.</i> | IIa | C |
| Lung transplantation: | | |
| <i>It is recommended that potentially eligible candidates are referred for LTx evaluation when they have an inadequate response to oral combination therapy, indicated by an intermediate-high or high risk or by a REVEAL risk score > 7.</i> | I | C |
| <i>It is recommended to list patients for LTx who present with a high risk of death or with a REVEAL risk score ≥ 10 despite receiving optimized medical therapy including s.c. or i.v. prostacyclin analogues.</i> | I | C |

▪ **Specific pulmonary arterial hypertension subsets:**

| Table 24-18: ESC Recommendations for Specific PAH subsets: | | |
|---|--------------|--------------|
| Recommendation | Class | Level |
| PAH associated with drugs and toxins: | | |

| | | |
|---|-----|---|
| Several drugs and toxins are associated with developing PAH or PVOD/PCH. Historically, certain appetite suppressants and toxic rapeseed oil were the most prominent examples, whereas methamphetamines, interferons, and some tyrosine kinase inhibitors are more common causes nowadays. | | |
| <i>It is recommended to make a diagnosis of drug- or toxin-associated PAH in patients who had relevant exposure and in whom other causes of PH have been excluded.</i> | I | C |
| <i>In patients with suspected drug- or toxin-associated PAH, it is recommended to immediately discontinue the causative agent whenever possible.</i> | I | C |
| <i>In patients who present with intermediate-/high-risk PAH at diagnosis, immediate PAH therapy should be considered.</i> | IIa | C |
| <i>Patients with low-risk PAH should be re-evaluated 3-4 months after discontinuing the suspected drug or toxin, and PAH therapy may be considered when the hemodynamics have not normalized.</i> | IIb | C |
| PAH associated with connective tissue disease: | | |
| PAH is a well-known pulmonary vascular complication of SSc, SLE, mixed CTD, and, rarely, dermatomyositis and Sjögren's syndrome. | | |
| <i>In patients with PAH associated with CTD, treatment of the underlying condition according to current guidelines is recommended.</i> | I | A |
| <i>In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended.</i> | I | C |
| PAH associated with HIV infection: | | |
| The use of highly active antiretroviral therapy (HAART), and advances in managing opportunistic infections have contributed to increased life expectancy. Therefore, the spectrum of complications has shifted towards other long-term conditions, including PAH. | | |

| | | |
|---|------------|----------|
| <i>In patients with PAH associated with HIV infection, antiretroviral treatment according to current guidelines is recommended.</i> | I | A |
| <i>In patients with PAH associated with HIV infection, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration comorbidities and drug-drug interactions.</i> | IIa | C |
| PAH associated with portal hypertension: | | |
| PAH associated with portal hypertension, commonly referred to as PoPH, develops in 2-6% of patients with portal hypertension, with or without liver disease. In PAH registries, PoPH represents 5-15% of the patients. The diagnosis of PoPH is based on the presence of otherwise unexplained pre-capillary PH in patients with portal hypertension <u>or</u> a portosystemic shunt. | | |
| <i>Echocardiography is recommended in patients with liver disease or portal hypertension with signs or symptoms suggestive of PH, and as a screening tool in patients evaluated for liver transplantation or transjugular portosystemic shunt.</i> | I | C |
| <i>It is recommended that patients with PAH associated with portal hypertension are referred to centres with expertise in managing both conditions.</i> | I | C |
| <i>In patients with PAH associated with portal hypertension, initial monotherapy should be considered, followed by sequential combination if necessary, taking into consideration the underlying liver disease and indication for liver transplantation.</i> | IIa | C |
| <i>Liver transplantation should be considered on an individual basis in patients with PAH associated with portal hypertension, as long as PVR is normal or near normal with PAH therapy.</i> | IIa | C |
| <i>Drugs approved for PAH are not recommended for patients with portal hypertension and unclassified PH (i.e. elevated mPAP, high CO, and a normal PVR).</i> | III | C |
| PAH with signs of Pulmonary veno-occlusive disease (PVOD): | | |

PVOD is a rare subtype of PAH characterized by progressive obstruction of small pulmonary veins leading to elevated pulmonary arterial pressure and right-sided heart failure. The pathophysiology of the disease remains poor. The proportion of patients with IPAH that fulfil the criteria for PVOD/PCH is 10%.

The clinical features are very non-specific and can resemble congestive heart failure, idiopathic PAH, and restrictive lung diseases such as pulmonary fibrosis.

The gold standard for diagnosis is a biopsy, which is risky and not advisable in pulmonary hypertension due to a high risk of procedure-related complications such as life-threatening bleeding.

No medical therapy is supported by evidence, and the only curative option is lung transplantation.

The prognosis is poor, and life expectancy is two years after symptom onset.

| | | |
|--|------------|----------|
| <i>A combination of clinical and radiological findings, ABG, PFTs, and genetic testing is recommended to diagnose PAH with signs of venous and/or capillary involvement (PVOD/PCH)</i> | I | A |
| <i>Identification of biallelic EIF2AK4 mutations is recommended to confirm a diagnosis of heritable PVOD/PCH.</i> | I | A |
| <i>Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is recommended as soon as the diagnosis is established.</i> | I | C |
| <i>In patients with PVOD/PCH, the use of drugs approved for PAH may be considered with careful monitoring of clinical symptoms and gas exchange.</i> | IIb | C |
| <i>Lung biopsy is not recommended to confirm a diagnosis of PVOD/PCH</i> | III | C |

- **PAH associated with adult congenital heart disease:**

- With a large left-to-right shunt (e.g., VSD, PDA, or less often ASD), PA pressure initially increases as a result of the increase in right-sided flow, PVR remaining initially low (Pressure= Flow × Resistance; an increase in flow leads to an increase in pressure).
- Over time, the increased pulmonary flow induces progressive pulmonary vascular disease and severe increase in PVR to a point that PVR approaches SVR, PA pressure approaches systemic pressure, and the shunt reverses and becomes directed right-to-left or bidirectional.

- The presence of PH in adults with CHD has a negative impact on the natural course of CHD, and worsens clinical status and overall outcome. A specific clinical classification is provided to better characterize PAH associated with adult CHD. Shunt closure (surgical or interventional) may only be considered in patients with prevalent systemic-to-pulmonary shunting without significantly increased PVR.

| Table 24-19: Clinical classification of PAH associated with congenital heart disease: | |
|---|---|
| (1) | <p>Eisenmenger syndrome:</p> <p><i>Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present. Closing the defects is contraindicated.</i></p> |
| (2) | <p>PAH associated with prevalent systemic-to-pulmonary shunts:</p> <ul style="list-style-type: none"> • Correctable • Non-correctable <p><i>Include moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.</i></p> |
| (3) | <p>PAH with small/coincidental defects:</p> <p><i>Markedly elevated PVR in the presence of cardiac defects considered hemodynamically non-significant (usually VSD < 1 cm and ASD < 2 cm), which themselves do not account for the development of elevated PVR. The clinical picture is very similar to IPAH. Closing the defects is contraindicated.</i></p> |
| (4) | <p>PAH after defect correction:</p> <p><i>Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant, post-operative, hemodynamic lesions.</i></p> |

- **Pediatric pulmonary hypertension:**

Pulmonary hypertension may present at all ages, including in infants and children. Pulmonary hypertension in childhood shares many common features with PH in adulthood. PH in neonates and infants is frequently associated with developmental lung diseases. In the absence of RCTs in pediatric PAH, recommended treatment algorithms are extrapolated from those in adults.

PH associated with left heart disease (Group 2)

PH-LHD represents the most prevalent form of PH, accounting for 65-80% of cases.

Among patients with LHD, PH and RV dysfunction are frequently present and associated with high mortality. This includes patients with HFrEF, HFmrEF, or HFpEF, left-sided valvular heart disease, and congenital/acquired cardiovascular conditions leading to postcapillary PH. This may produce an increase in LA pressure with passive backward transmission of pressure to the pulmonary circulation. As a result, PA pressure rises. In this case:

- PCWP is elevated (> 15 mmHg).
- PVR is < 3 WU.
- The transpulmonary gradient, (i.e., mean PA pressure - PCWP), is < 12 mmHg.
- Diastolic PA pressure is passively increased and is equal to PCWP or is up to 7 mmHg higher than PCWP.

▪ **Diagnosis:**

In patients with LHD, symptoms (e.g., exertional dyspnea) and physical signs of PH (e.g., peripheral edema) frequently overlap with those of the underlying left heart condition and are mostly nonspecific. Given the complexity and variability of cardiopulmonary hemodynamics in patients with LHD, the distinction between post- and pre-capillary PH and the diagnosis of PH-LHD vs. other forms of PH can be challenging. Diagnostic clues in the evaluation of suspected PH in LHD include: **(1)** diagnosis and control of the underlying LHD; **(2)** evaluation for PH and patient phenotyping; and **(3)** invasive hemodynamic evaluation, when indicated.

For phenotyping, a combination of variables may help to determine the likelihood of LHD, and HFpEF in particular, versus other causes of PH.

Table 24-20: Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension

| Feature | PH-LHD unlikely | Intermediate probability | PH-LHD likely |
|---------|-----------------|--------------------------|---------------|
| Age | < 60 years | 60-70 years | > 70 years |

| | | | |
|---|--|---|---|
| Obesity, HTN, dyslipidemia, glucose intolerance/DM | No factors | 1-2 factors | > 2 factors |
| Presence of known LHD | No | Yes | Yes |
| Previous cardiac intervention | No | No | Yes |
| Atrial fibrillation | No | Paroxysmal | Permanent/persistent |
| Structural LHD | No | No | Present |
| ECG | Normal or RV strain | Mild LVH | LBBB or LVH |
| Echocardiography | No LA dilation E/e' < 13 | No LA dilation Grade < 2 mitral flow | - LAVI > 34 mL/m ² - LVH - Grade > 2 mitral flow |
| CPET | High VE/VCO ₂ slope No EOv | Elevated VE/VCO ₂ slope EOv | - Mildly elevated - VE/VCO ₂ slope - EOv |
| Cardiac MRI | No left heart abnormalities | | - LVH - LA dilation (strain or LA/RA > 1) |

▪ **Therapy:**

| Table 24-21: ESC Recommendations for pulmonary hypertension associated with left heart disease: | | |
|---|--------------|--------------|
| Recommendation | Class | Level |
| <i>In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH.</i> | I | A |
| <i>RHC is recommended for suspected PH in patients with LHD, if it aids management decisions.</i> | I | C |

| | | |
|--|------------|----------|
| <i>RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair.</i> | I | C |
| <i>For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended.</i> | I | C |
| <i>In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR > 5 WU), an individualized approach to treatment is recommended.</i> | I | C |
| <i>When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended.</i> | I | C |
| <i>In patients with PH at RHC, a borderline PAWP (13-15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH.</i> | IIb | C |
| <i>Drugs approved for PAH are not recommended in PH-LHD ⁽¹⁾</i> | III | A |
| <i>The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended ⁽²⁾</i> | III | C |

PH associated with lung diseases and/or hypoxia (group 3)

Pulmonary hypertension is frequently observed in patients with COPD and/or emphysema, interstitial lung disease (ILD), combined pulmonary fibrosis and emphysema (CPFE), and hypoventilation syndromes.

At high altitude (> 2500 m), hypoxia-induced PH is thought to affect > 5% of the population. The development of PH being related to geography and genetic factors.

Even non-severe PH in lung disease negatively impacts symptoms and survival, and is associated with increased hospitalization.

(1) Safety concerns have been identified when ERAs are used in patients with HF (HFpEF and HFrEF, with or without PH) and when sildenafil is used in patients with persistent PH after correction of valvular heart disease.

(2) ESC guidelines stated that: No recommendation can be given for or against the use of PDE5is in patients with HFpEF and combined post- and pre-capillary PH.

▪ **Diagnosis:**

In patients with lung disease, symptoms of PH (especially exertional dyspnea) overlap with those of the underlying condition. Key parts of evaluating suspected PH in lung disease include integrating: **(1)** Presence or absence of risk factors for PAH, CTEPH, or LHD; **(2)** Clinical features, including disease trajectory (e.g. rapid recent deterioration vs. gradual change over years, and oxygen requirements); **(3)** PFTs, including DLCO and blood gas analysis; **(4)** NT-proBNP measurements, ECG, and echocardiography; and **(5)** Cross-sectional imaging with contrast-enhanced CT, SPECT, or V/Q lung scan and, in selected cases, cardiac MRI to assess the need for RHC.

▪ **Therapy:**

| Table 24-22: ESC Recommendations for pulmonary hypertension associated with lung disease and/or hypoxia: | | |
|---|-------|-------|
| Recommendation | Class | Level |
| <i>If PH is suspected in patients with lung disease, it is recommended that echocardiography be performed ⁽¹⁾ and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging.</i> | I | C |
| <i>In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended ⁽²⁾</i> | I | C |
| <i>In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation</i> | I | C |
| <i>In patients with lung disease and severe PH, an individualized approach to treatment is recommended.</i> | I | C |
| <i>It is recommended to refer eligible patients with lung disease and PH for LTx evaluation.</i> | I | C |
| <i>In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions.</i> | I | C |
| <i>Inhaled treprostinil may be considered in patients with PH associated with ILD.</i> | IIb | B |

(1) Assessments should ideally be made when the patient is clinically stable, as exacerbations can significantly raise PA pressure.

(2) This recommendation does not apply to patients with end-stage lung disease who are not considered candidates for LTx.

| | | |
|--|------------|----------|
| <i>The use of ambrisentan is not recommended in patients with PH associated with idiopathic pulmonary fibrosis.</i> | III | B |
| <i>The use of riociguat is not recommended in patients with PH associated with idiopathic interstitial pneumonia.</i> | III | B |
| <i>The use of PAH medication is not recommended in patients with lung disease and non-severe PH ⁽¹⁾</i> | III | C |
| <i>PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres).</i> | IIb | C |
| <i>The use of PDE5is in patients with ILD and non-severe PH is not recommended.</i> | III | C |

Chronic Thrombo-embolic Pulmonary Hypertension (group 4)

Approximately 4% of patients who develop acute PE do not fully resolve their thrombus burden and go on to develop chronic PH. This often occurs after single PE episodes. Most often, the thrombus involves the main pulmonary artery or the proximal arteries (80%), with small-vessel arteriopathy and thrombosis that subsequently occur and contribute to disease progression.

All patients whose symptoms can be attributed to post-thrombo-embolic fibrotic obstructions within the PA are considered to have chronic thromboembolic pulmonary disease (CTEPD) with or without PH; CTEPH remains the preferred term for patients with PH.

Pulmonary hypertension in this setting is not only a consequence of PA obstruction by organized fibrotic clots, but can also be related to the associated microvasculopathy.

In those patients without PH at rest, breathlessness could be due to exercise PH and/or increased dead space ventilation.

Excluding ventilator limitation, deconditioning and psychogenic hyperventilation syndrome by CPET and LV myocardial or valvular disease by echocardiography is of utmost importance when making therapeutic decisions in patients with CTEPD without PH.

▪ Diagnosis:

(1) This does not include inhaled treprostinil, which may be considered in patients with PH associated with ILD, irrespective of PH severity.

CTEPH is a common and important cause of PH, with a distinct management strategy. Thus, the possibility of CTEPH should be carefully considered in all patients with PH.

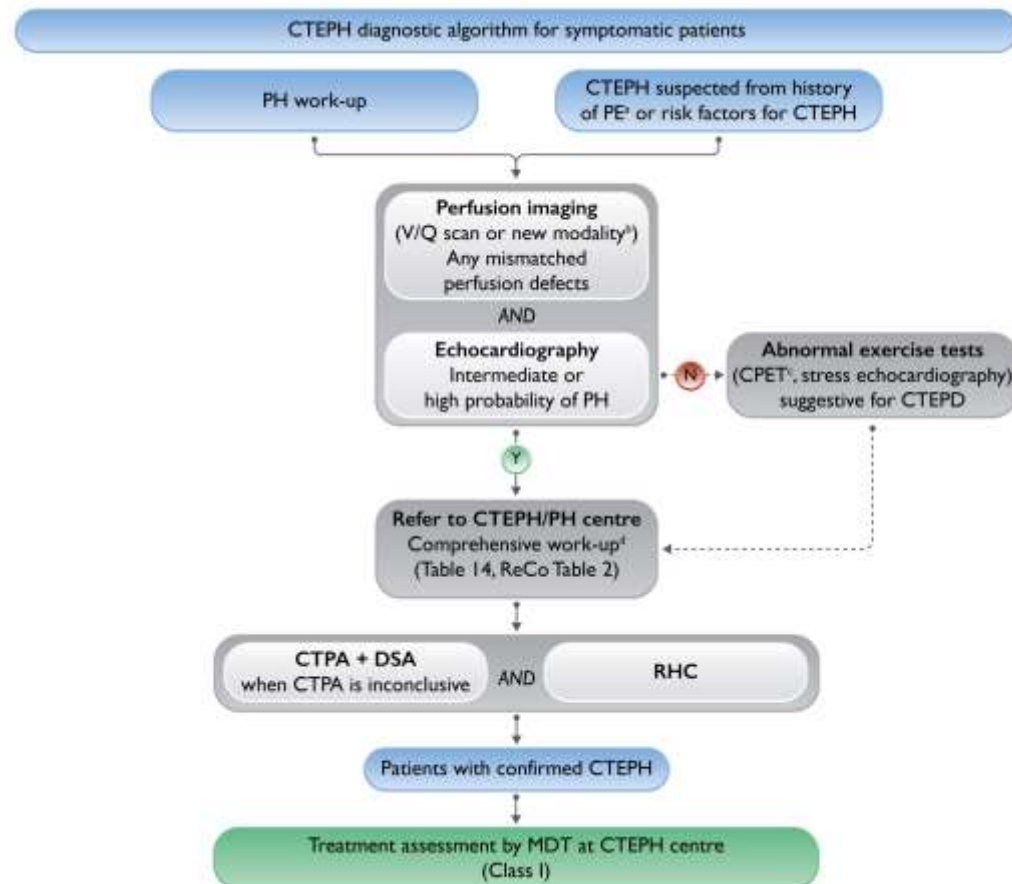


Figure 24-9: Diagnostic strategy in chronic thrombo-embolic pulmonary hypertension. (A) CTEPH suspected from history of PE, including elevated sPAP on echocardiography and signs suggesting CTEPH on CTPA performed at the time of the acute PE. **(B)** Alternative perfusion imaging techniques -such as iodine subtraction mapping, DECT, and MRI perfusion- are currently under evaluation. **(C)** Typical pattern, including low PETCO₂, high VE/VCO₂, low VO₂/HR, and low peak VO₂. **(D)** Comprehensive work-up after 3 months of therapeutic anticoagulation or sooner in unstable or rapidly deteriorating patients. Ideally, CTPA, DSA, and RHC are performed in CTEPH centres, but they are sometimes performed in PH centres, depending on the country and organization. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

- **Therapy:**

The CTEPH treatment algorithm includes a multimodal approach of combinations of pulmonary endarterectomy (PEA), Balloon pulmonary angioplasty (BPA), and medical therapies to target the mixed anatomical lesions: proximal, distal, and microvasculopathy, respectively.

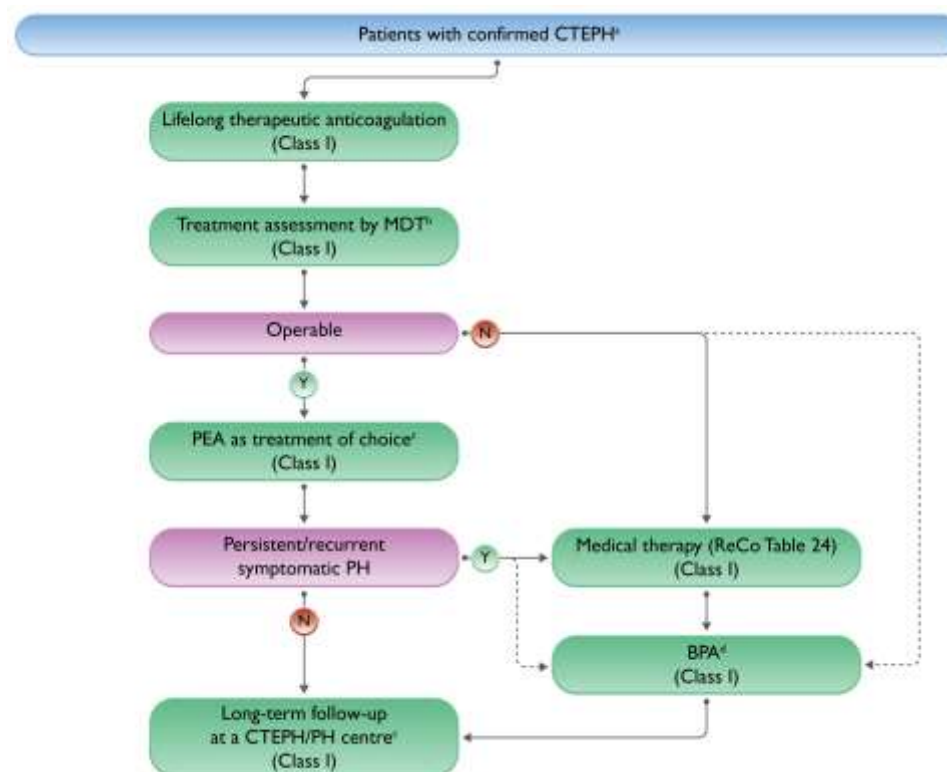


Figure 24-10: Management strategy in chronic thrombo-embolic pulmonary hypertension. (A) Selected symptomatic patients with CTEPD without PH can also be treated by PEA and BPA. **(B)** MDT meeting can be virtual. **(C)** Treatment assessment may differ, depending on the level of expertise in PEA and BPA. **(D)** For inoperable patients with PVR > 4 WU, medical therapy should be considered prior to BPA; there are limited data on BPA as first-line therapy. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

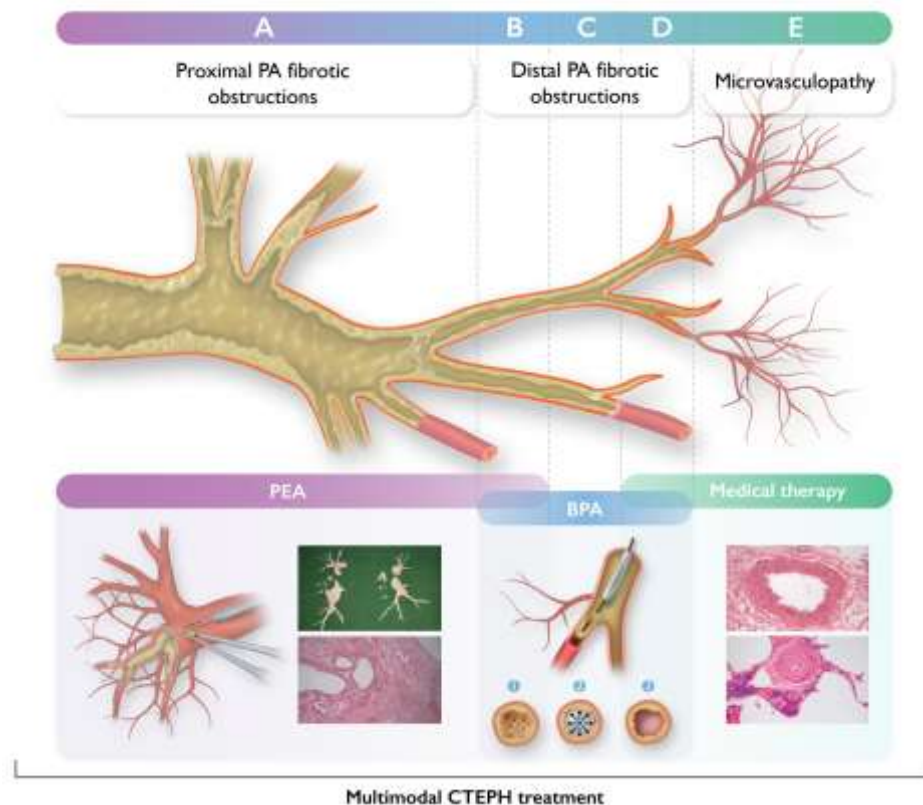


Figure 24-11: Overlap in treatments/multimodality approaches in CTEPH.

Top panels: (A) Proximal PA fibrotic obstructions (vessel diameter 10-40 mm). (B) Distal segmental and subsegmental PA fibrotic obstruction potentially suitable for both PEA and BPA interventions (vessel diameter 2-10 mm). (C) Distal subsegmental PA fibrotic obstructions form a web-lesion in a subsegmental branch of the PA suitable for BPA interventions (vessel diameter 0.5-5 mm). (D) Distal subsegmental PA fibrotic obstructions form web-like lesions, which might be accompanied by microvasculopathy (vessel diameter < 0.5 mm). (E) Microvasculopathy (vessel diameter < 0.05 mm) treated with medical therapy.

Bottom panels: (A) bottom left: PEA; vessel diameter (0.2-3 cm). The right PA is opened and the suction dissector is introduced between the artery wall and fibrosis. Following the inside of the artery down to segmental and subsegmental levels, the fibrotic material is subsequently freed from the wall and removed with forceps. (A) bottom right: PEA specimen with 'tails' to subsegmental branches of the PA; cross-section of partially organized and permeabilized thrombotic lesion of the large PA dissected during PEA. (B, C, D) The wire is introduced between the fibrotic material (1), then the balloon is inflated, leading to a rupture of the web (2). Fibrotic material is connected to the vessel wall (3). (E) Small muscular PA displaying eccentric intimal fibrosis involving intimal thickening and proliferation-target for medical therapies. **Source:** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Table 24-23: ESC Recommendations for chronic thrombo-embolic pulmonary hypertension and chronic thrombo-embolic pulmonary disease without pulmonary hypertension:

| Recommendation | Class | Level |
|---|--------------|--------------|
| CTEPH: | | |
| <i>Lifelong, therapeutic doses of anticoagulation are recommended in all patients with CTEPH.</i> | I | C |
| <i>Antiphospholipid syndrome testing is recommended in patients with CTEPH.</i> | I | C |
| <i>In patients with CTEPH and antiphospholipid syndrome, anticoagulation with VKAs is recommended.</i> | I | C |
| <i>It is recommended that all patients with CTEPH are reviewed by a CTEPH team for the assessment of multimodality management.</i> | I | C |
| <i>PEA is recommended as the treatment of choice for patients with CTEPH and fibrotic obstructions within pulmonary arteries accessible by surgery.</i> | I | B |
| <i>BPA is recommended in patients who are technically inoperable <u>or</u> have residual PH after PEA and distal obstructions amenable to BPA.</i> | I | B |
| <i>BPA may be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk-benefit ratio for PEA.</i> | IIb | C |
| <i>In patients with CTEPH who candidates for BPA are, medical therapy should be considered prior to the intervention.</i> | IIa | C |
| <i>Riociguat is recommended for symptomatic patients with inoperable CTEPH <u>or</u> persistent/recurrent PH after PEA.</i> | I | B |
| <i>Long-term follow-up is recommended after PEA and BPA, as well as for patients with CTEPH established on medical therapy.</i> | I | C |
| <i>A multimodality approach should be considered for patients with persistent PH after PEA and for patients with inoperable CTEPH.</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>Treprostinil s.c. may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA.</i> | IIb | B |
| <i>Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH.</i> | IIb | B |
| <i>In patients with inoperable CTEPH, a combination of sGC stimulator/PDE5i, ERA, or parenteral prostacyclin analogues may be considered.</i> | IIb | C |
| CTEPD without PH: | | |
| <i>In patients with CTEPD without PH, long-term anticoagulant therapy should be considered on an individual basis⁽¹⁾.</i> | IIa | C |
| <i>PEA or BPA should be considered in selected symptomatic patients with CTEPD without PH</i> | IIa | C |

PH with unclear and/or multifactorial mechanisms (group 5)

PH with unclear and/or multifactorial mechanisms includes several conditions that may be complicated by complex and sometimes overlapping pulmonary vascular involvement. In the absence of positive RCTs studying the use of PAH drugs for this cohort, treating the underlying disorder remains the standard of care

Table 24-24: Pulmonary hypertension with unclear and/ or multifactorial mechanisms:

| | |
|-------------------------------------|---|
| 1. Haematological disorders: | <ul style="list-style-type: none"> ○ Inherited and acquired chronic haemolytic anaemia: <ul style="list-style-type: none"> - Sickle cell disease - β-thalassaemia - Spherocytosis - Stomatocytosis - Autoimmune disorders |
|-------------------------------------|---|

(1) Long-term anticoagulant therapy is recommended when the risk of PE recurrence is intermediate or high, or when there is no history of venous thrombo-embolism.

| | |
|---|--|
| | <ul style="list-style-type: none"> ○ Chronic myeloproliferative disorders: <ul style="list-style-type: none"> - Chronic myelogenous leukaemia - Polycythaemia vera - Idiopathic myelofibrosis - Essential thrombocytopenia |
| 2. Systemic disorders: | Sarcoidosis, Pulmonary Langerhans's cell histiocytosis, Neurofibromatosis type 1 |
| 3. Metabolic disorders: | Glycogen storage disease, Gaucher disease |
| 4. Chronic renal failure with/ without haemodialysis | |
| 5. Pulmonary tumour thrombotic microangiopathy | |
| 6. Fibrosis mediastinitis | |

Important trials in pulmonary arterial hypertension:

Table 24-25: Clinical trials in pulmonary hypertension:

| Trial (date) | Summary |
|-------------------------------|---|
| BREATHE - 1 (2002) | <p>Aim: To investigate the effect of bosentan on exercise capacity in patients with PAH (WHO class IV) and to compare two doses (125 and 250 mg).</p> <p>Study: 213 patients with PAH (primary or associated with connective-tissue disease) were randomly assigned to receive placebo or to receive 62.5 mg of bosentan twice daily for 4 weeks followed by either of two doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks. Bosentan is beneficial in patients with PAH and is well tolerated at a dose of 125 mg twice daily.</p> |
| BREATHE- 2 | <p>Aim: To investigate the efficacy and safety of the combination of bosentan and epoprostenol in the treatment of patients with severe PAH.</p> |

| | |
|-------------------------|---|
| (2004) | <p>Study: 30 patients were randomized in a 2 to 1 fashion to receive epoprostenol with bosentan or epoprostenol alone over a 16-week period. The dose of epoprostenol was kept similar in both groups. The trial failed to show any significant difference between the groups with respect to hemodynamics or 6-minute walk distance. However, 2 of the patients randomized to the combination therapy died, and a third patient had worsening pulmonary hypertension requiring them to drop out.</p> |
| AMBITION (2015) | <p>Aim: To investigate the efficacy and safety of initial combination therapy with oral, once-daily ambrisentan and tadalafil in patients with PAH.</p> <p>Study: 253 participants with WHO functional class II or III symptoms of PAH who had not previously received treatment were randomly assigned to receive initial combination therapy with ambrisentan (10 mg) plus tadalafil (40 mg), <u>or</u> ambrisentan (10 mg) plus placebo, <u>or</u> tadalafil (40 mg) plus placebo, all administered once daily. The primary endpoint in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy.</p> |
| FREEDOM-M (2013) | <p>Aim: To evaluate the safety and efficacy of treprostinil as initial treatment for de novo PAH.</p> <p>Study: 349 patients not receiving ERA or PDE5i background therapy were randomized to treprostinil or placebo. The primary analysis population (modified intent-to-treat) included 228 patients (treprostinil, n=151; placebo, n=77) with access to 0.25-mg treprostinil tablets at randomization. The primary endpoint was change from baseline in 6-minute walk distance at week 12. Oral treprostinil improves exercise capacity in PAH patients not receiving other treatment. Oral treprostinil could provide a convenient, first-line prostacyclin treatment option for PAH patients not requiring more intensive therapy.</p> |
| IMPRES (2013) | <p>Aim: To evaluate the safety, tolerability, and efficacy of imatinib in patients with advanced PAH who were receiving at least 2 PAH therapies.</p> |

| | |
|-----------------------|--|
| | <p>Study: 202 patients with $PVR \geq 800 \text{ dyne.s.cm}^{(-5)}$ symptomatic on ≥ 2 PAH therapies were randomized to receive to imatinib (starting dose of 200 mg once daily) or placebo. The primary outcome was change in 6-minute walk distance. Imatinib improved exercise capacity and hemodynamics in patients with advanced PAH, but serious adverse events and study drug discontinuations were common.</p> |
| GRIPHON (2015) | <p>Aim: To investigate the safety and efficacy of selexipag in patients with PAH who were not receiving therapy at baseline and those who were already receiving one or two therapies for the disease at baseline.</p> <p>Study: 1156 patients with PAH were randomly assigned to receive placebo or selexipag in individualized doses (max dose, 1600 μg twice daily). Patients were eligible for enrollment if they were not receiving treatment for PAH or if they were receiving a stable dose of an ERA, a PDE5is, or both. The primary end point was a composite of death from any cause or a complication related to PAH up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo). Among patients with PAH, the risk of the primary composite end point of death or a complication related to PAH was significantly lower with selexipag than with placebo. There was no significant difference in mortality between the two study groups.</p> |

References and suggested readings:

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Section

VIII

Systemic Vascular Disorders

TO THE POINT

Chapter 25:

Aortic disease

The normal and the ageing aorta

The aorta is the ultimate conduit, carrying, in an average lifetime, almost 200 million litres of blood to the body. It is divided by the diaphragm into the thoracic and abdominal aorta.

In addition to the conduit function, the aorta plays an important role in the control of systemic vascular resistance and heart rate, via pressure-responsive receptors (baroreceptors) located in the ascending aorta and aortic arch. An increase in aortic pressure results in a decrease in heart rate and systemic vascular resistance, whereas a decrease in aortic pressure has the opposite effect. Through its elasticity, the aorta has the role of a 'second pump' (***Windkessel function***) during diastole, which is of the utmost importance, not only for coronary perfusion.

The aortic wall is composed histologically of three layers:

- Thin inner tunica intima lined by the endothelium;
- Thick media characterized by concentric sheets of elastic and collagen fibres with the border zone of the lamina elastica interna and -externa, as well as smooth muscle cells; and
- The outer tunica adventitia containing mainly collagen, vasa vasorum, and lymphatics.

In healthy adults, aortic diameters do not usually exceed 40 mm and taper gradually downstream. They are variably influenced by several factors including: age, gender, body size [height, weight, body surface area] and blood pressure. In this regard, the rate of aortic expansion is about 0.9 mm in men and 0.7 mm in women for each decade of life.

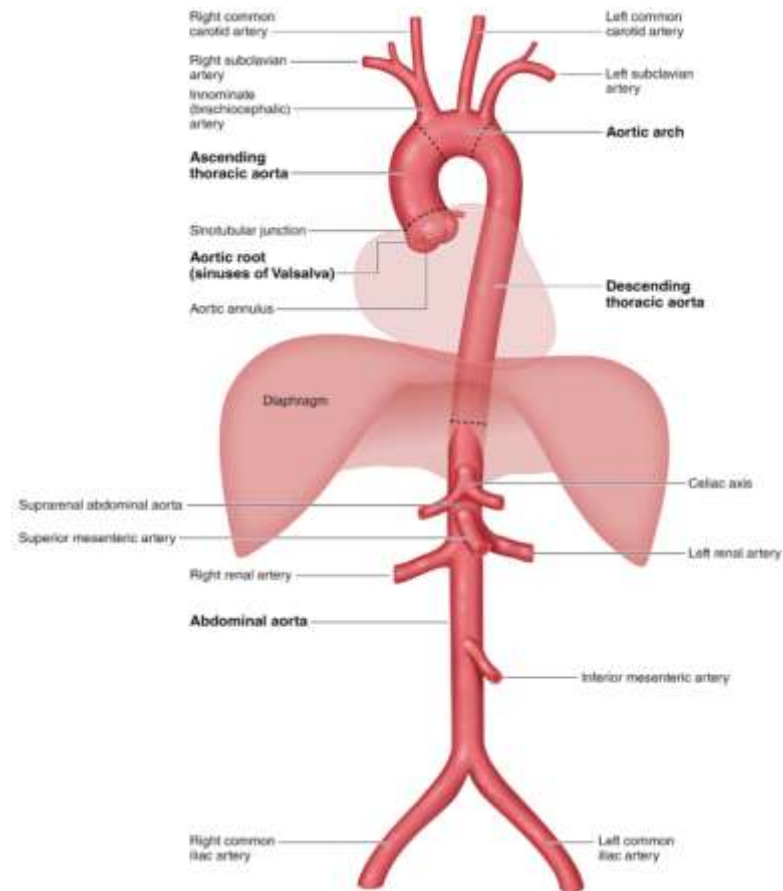


Figure 25-1: Segments of the ascending and descending aorta. The aorta can be divided into 5 main anatomic segments: (1) the root or sinus segment, which extends from the aortic valve annulus to the sinotubular junction; (2) the ascending thoracic aorta, which extends from the sinotubular junction to the innominate artery; (3) the aortic arch, which extends from the innominate to the left subclavian artery; (4) the descending thoracic aorta, which extends from the left subclavian artery to the diaphragm; and (5) the abdominal aorta, which extends from the diaphragm to the level of the aortic bifurcation.

Assessment of the aorta:

▪ **Clinical examination:**

While aortic diseases may be clinically silent in many cases, a broad range of symptoms may be related to different aortic diseases:

- Acute deep, aching or throbbing chest or abdominal pain that can spread to the back, buttocks, groin or legs, suggestive of AD or other AAS, and best described as 'feeling of rupture'.
- Cough, shortness of breath, or difficult or painful swallowing in large TAAs.
- Constant or intermittent abdominal pain or discomfort, a pulsating feeling in the abdomen, or feeling of fullness after minimal food intake in large AAAs.
- Stroke, transient ischemic attack, or claudication secondary to aortic atherosclerosis.
- Hoarseness due to left laryngeal nerve palsy in rapidly progressing lesions.

▪ **Laboratory testing:** Laboratory testing plays a minor role in the diagnosis of acute aortic diseases but is useful for differential diagnoses.

▪ **Imaging:**

○ **Transthoracic echocardiography (TTE):**

Although TTE is not the technique of choice for full assessment of the aorta, it is useful for the diagnosis and follow-up of some aortic segments. TTE is the most frequently used technique for measuring proximal aortic segments. The aortic root is visualized in the parasternal long-axis and modified apical five-chamber views; however, in these views the aortic walls are seen with suboptimal lateral resolution.

○ **Transoesophageal echocardiography:**

The relative proximity of the esophagus and the thoracic aorta permits high-resolution images with higher-frequency TOE. Owing to interposition of the right bronchus and trachea, a short segment of the distal ascending aorta, just before the innominate artery, remains invisible (a 'blind spot').

○ **Abdominal ultrasound:**

Abdominal ultrasound remains the mainstay imaging modality for abdominal aortic diseases because of its ability to accurately measure the aortic size, to detect wall lesions such as mural thrombus or plaques, and because of its wide availability, painlessness, and low cost.

Duplex ultrasound provides additional information on aortic flow. Colour Doppler is of great interest in the case of abdominal aorta dissection, to detect perfusion of both false and true lumen and potential re-entry sites or obstruction of tributaries (e.g. the iliac arteries).

○**Computed tomography:**

Computed tomography plays a central role in the diagnosis, risk stratification, and management of aortic diseases. Its advantages over other imaging modalities include the short time required for image acquisition and processing, the ability to obtain a complete 3D dataset of the entire aorta, and its widespread availability.

○**Positron emission tomography/computed tomography (PET-CT):**

The advantages of PET may be combined with CT imaging with good resolution and can be used to detect *vascular inflammation in large vessels*.

○**Magnetic resonance imaging (MRI):**

With its ability to delineate the intrinsic contrast between blood flow and vessel wall, MRI is well suited for diagnosing aortic diseases.

In the acute setting, MRI is limited because it is less accessible, it is more difficult to monitor unstable patients during imaging, and it has longer acquisition times than CT.

MRI does not require ionizing radiation or iodinated contrast and is therefore highly suitable for serial follow-up studies in (younger) patients with known aortic disease.

| Table 25-1: Comparison of methods for imaging the aorta ⁽¹⁾ : | | | | | |
|--|-----|-----|----|-----|-------------|
| | TTE | TOE | CT | MRI | Aortography |

(1) (+) means a positive remark and (-) means a negative remark. The number of signs indicates the estimated potential value

| | | | | | |
|----------------------------|-----|-----|-----|-----|-----|
| Ease of use | +++ | ++ | +++ | ++ | + |
| Diagnostic reliability | + | +++ | +++ | +++ | ++ |
| Bedside/interventional use | ++ | ++ | - | - | ++ |
| Serial examinations | ++ | + | ++ | +++ | - |
| Aortic wall visualization | + | +++ | +++ | +++ | - |
| Cost | - | - | -- | --- | --- |
| Radiation | 0 | 0 | --- | - | -- |
| Nephrotoxicity | 0 | 0 | --- | -- | --- |

Table 25-2: Diagnostic value of different imaging modalities in acute aortic syndromes ⁽¹⁾:

| | TTE | TOE | CT | MRI |
|-------------------------------|------------------|------------|-----------|------------|
| Ascending Aortic dissection | ++ | +++ | +++ | +++ |
| Aortic arch dissection | + | + | +++ | +++ |
| Descending aortic dissection | + | +++ | +++ | +++ |
| Size | ++ | +++ | +++ | +++ |
| Mural thrombus | + | +++ | +++ | +++ |
| Intramural thrombus | + | +++ | ++ | +++ |
| Penetrating thrombus | ++ | +++ | +++ | +++ |
| Involvement of aortic plaques | + ⁽²⁾ | (+) | +++ | +++ |

Table 25-3: Details required from imaging in acute aortic dissection:

(1) (+++)= excellent, (++)= moderate, (+)= poor

(2) Can be improved when combined with vascular ultrasound (carotid, subclavian, vertebral, celiac, mesenteric and renal arteries)

| |
|---|
| Aortic dissection |
| Extent of the disease according to the aortic anatomic segmentation |
| Visualization of intimal flap |
| Identification grading, and mechanism of aortic valve regurgitation |
| Identification of the false and true lumens (if present) |
| Localization of entry and re-entry tears (if present) |
| Identification of antegrade and/or retrograde aortic dissection |
| Involvement of side branches |
| Detection of malperfusion (low flow or no flow) |
| Detection of organ ischaemia (brain, myocardium, bowels, kidneys, etc.) |
| Detection of pericardial effusion and its severity |
| Detection and extent of pleural effusion |
| Detection of peri-aortic bleeding |
| Signs of mediastinal bleeding |
| Intramural haematoma |
| Localization and extent of aortic wall thickening |
| Co-existence of atheromatous disease (calcium shift) |
| Presence of small intimal tears |
| Penetrating aortic ulcer |
| Localization of the lesion (length and depth) |
| Co-existence of intramural haematoma |
| Involvement of the peri-aortic tissue and bleeding |
| Thickness of the residual wall |

In all cases

Co-existence of other aortic lesions: aneurysms, plaques, inflammatory disease signs, etc.

Table 25-4: ESC and ACC Recommendations for imaging the aorta:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>It is recommended that diameters be measured at pre-specified anatomical landmarks, perpendicular to the longitudinal axis ⁽¹⁾.</i> | I | C |
| <i>In the case of repetitive imaging of the aorta over time, to assess change in diameter, it is recommended that the imaging modality with the lowest iatrogenic risk be used.</i> | I | C |
| <i>In the case of repetitive imaging of the aorta over time to assess change in diameter, it is recommended that the same imaging modality be used, with a similar method of measurement.</i> | I | C |
| <i>It is recommended that all relevant aortic diameters and abnormalities be reported according to the aortic segmentation.</i> | I | C |
| <i>It is recommended that renal function, pregnancy, and history of allergy to contrast media be assessed, in order to select the optimal imaging modality of the aorta with minimal radiation exposure, except for emergency cases.</i> | I | C |
| <i>The risk of radiation exposure should be assessed, especially in younger adults and in those undergoing repetitive imaging.</i> | Ila | B |
| <i>When performing CT or MR imaging, it is recommended that the root and ascending aortic diameters be measured from inner-edge to inner-edge, using an ECG-synchronized technique. If there are aortic wall abnormalities, such as atherosclerosis or discrete wall thickening, the outer-edge to outer-edge diameter should be reported</i> | I | C |

(1) In cases of asymmetric or oval contour, the longest diameter and its perpendicular diameter should be reported.

| | | |
|--|------------|----------|
| <i>In patients with known or suspected aortic disease, the aortic root diameter should be recorded as maximum sinus to sinus measurement. In the setting of known asymmetry, multiple measurements should be reported, and both short- and long-axis images of the root should be obtained to avoid underestimation of the diameter.</i> | I | C |
| <i>When performing echocardiography,</i> | | |
| <i>- It is reasonable to measure the aorta from leading-edge to leading-edge, perpendicular to the axis of blood flow.</i> | IIa | C |
| <i>- Using inner-edge to inner-edge measurements may also be considered, particularly on short-axis imaging.</i> | IIb | C |
| <i>In patients with known or suspected aortic disease, it is reasonable that a dilated root or ascending aorta be indexed to patient height or BSA, to aid in clinical risk assessment.</i> | IIa | C |

Assessment of aortic stiffness:

Arterial walls stiffen with age. Aortic stiffness is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall, and is increasingly recognized as a surrogate endpoint for cardiovascular disease.

Aortic stiffness has independent predictive value for all-cause and cardiovascular mortality, fatal and non-fatal coronary events, and fatal strokes in patients with various levels of cardiovascular risk, with a higher predictive value in subjects with a higher baseline cardiovascular risk.

Several non-invasive methods are currently used to assess aortic stiffness, such as pulse wave velocity and augmentation index. Increased arterial stiffness results in increased speed of the pulse wave in the artery.

Carotid-femoral pulse wave velocity is the ‘gold standard’ for measuring aortic stiffness, given its simplicity, accuracy, reproducibility, and strong predictive value for adverse outcomes.

Recent hypertension guidelines have recommended measurement of arterial stiffness as part of a comprehensive evaluation of patients with hypertension, in order to detect large artery stiffening with high predictive value and reproducibility.

Treatment options:

▪ **Principles of medical therapy:**

The main aim of medical therapy in this condition is to reduce shear stress on the diseased segment of the aorta by reducing blood pressure and cardiac contractility. A large number of patients with aortic diseases have comorbidities such as CAD, chronic kidney disease, DM, dyslipidaemia, hypertension, etc. Therefore, treatment and prevention strategies must be similar to those indicated for the above diseases.

Cessation of smoking is important, as studies have shown that self-reported current smoking induced a significantly faster AAA expansion (by approximately 0.4 mm/year).

▪ **Endovascular therapy:**

Thoracic endovascular aortic repair aims at excluding an aortic lesion (i.e. aneurysm or FL after AD) from the circulation by the implantation of a membrane-covered stent-graft across the lesion, in order to prevent further enlargement and ultimate aortic rupture.

In TEVAR, vascular complications at the puncture site, as well as aortic and neurological complications, and/or endoleaks have been reported. An endoleak results in the persistence of blood flow outside the graft and within the aneurysm sac, preventing its complete thrombosis. Consequently, patients with endografts require lifelong surveillance imaging to monitor for the appearance of endoleaks.

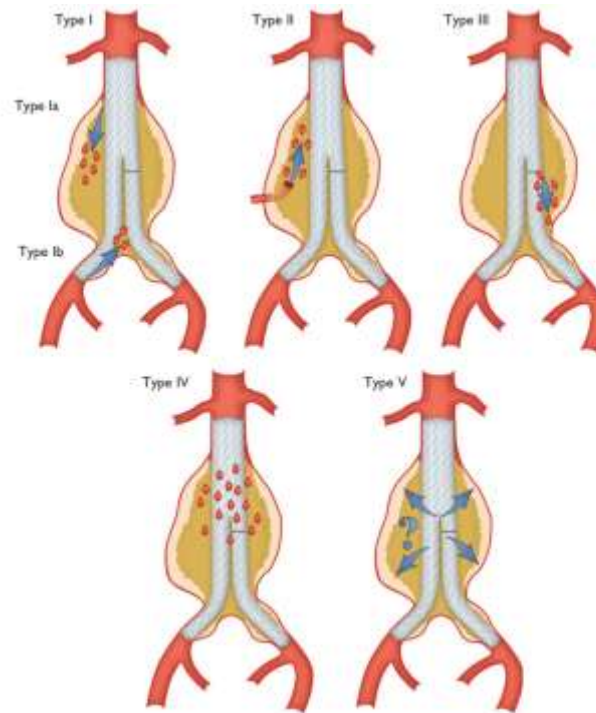


Figure 25-2: Classification of endoleaks.

Type I: Leak at graft attachment site above, below, or between graft components (**Ia**): proximal attachment site; (**Ib**): distal attachment site).

Type II: Aneurysm sac filling retrogradely via single (**IIa**) or multiple branch vessels (**IIb**).

Type III: Leak through mechanical defect in graft, mechanical failure of the stent-graft by junctional separation of the modular components (**IIIa**), or fractures or holes in the endograft (**IIIb**).

Type IV: Leak through graft fabric as a result of graft porosity.

Type V: Continued expansion of aneurysm sac without demonstrable leak on imaging (endotension, controversial).

Source: 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases modified from White GH, May J, Petrasek P. Semin Interv Cardiol.2000;5:35–46.

| Table 25-5: ESC Recommendations for (Thoracic) endovascular aortic repair ((T)EVAR): | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended that the indication for TEVAR or EVAR be decided on an individual basis, according to anatomy, pathology, comorbidity and anticipated durability, of any repair, using a multidisciplinary approach.</i> | I | C |
| <i>A sufficient proximal and distal landing zone of at least 2 cm is recommended for the safe deployment and durable fixation of TEVAR.</i> | I | C |
| <i>In case of aortic aneurysm, it is recommended to select a stent-graft with a diameter exceeding the diameter of the landing zones by at least 10–15% of the reference aorta.</i> | I | C |
| <i>During stent graft placement, invasive blood pressure monitoring and control (either pharmacologically or by rapid pacing) is recommended.</i> | I | C |
| <i>Preventive cerebrospinal fluid (CSF) drainage should be considered in high-risk patients.</i> | IIa | C |

▪ **Surgery:**

| Table 25-6: ESC Recommendations for surgical techniques in aortic diseases: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>Cerebrospinal fluid drainage is recommended in surgery of the thoraco-abdominal aorta, to reduce the risk of paraplegia.</i> | I | B |
| <i>Aortic valve repair, using the re-implantation technique or remodelling with aortic annuloplasty, is recommended in young patients with aortic root dilation and tricuspid aortic valves</i> | I | C |
| <i>For repair of acute Type A AD, an open distal anastomotic technique avoiding aortic clamping (hemiarch/complete arch) is recommended.</i> | I | C |

| | | |
|---|------------|----------|
| <i>In patients with connective tissue disorders requiring aortic surgery, the replacement of aortic sinuses is indicated.</i> | I | C |
| <i>Selective antegrade cerebral perfusion should be considered in aortic arch surgery, to reduce the risk of stroke</i> | Ila | B |
| <i>The axillary artery should be considered as first choice for cannulation for surgery of the aortic arch and in aortic dissection.</i> | Ila | C |
| <i>Left heart bypass should be considered during repair of the descending aorta or the thoraco-abdominal aorta, to ensure distal organ perfusion.</i> | Ila | C |

Acute thoracic aortic syndromes

Definition:

Acute aortic syndromes are defined as emergency conditions with similar clinical characteristics involving the aorta. There is a common pathway for the various manifestations of AAS that eventually leads to a breakdown of the intima and media. This may result in intramural hematoma (IMH), Penetrating aortic ulcer (PAU), or in separation of aortic wall layers, leading to AD or even thoracic aortic rupture.

Pathology and classification:

Acute aortic syndromes occur when either a tear or an ulcer allows blood to penetrate from the aortic lumen into the media or when a rupture of vasa vasorum causes a bleed within the media.

The inflammatory response to blood in the media may lead to aortic dilation and rupture.

Acute AD (< 14 days) is distinct from **sub-acute** (15-90 days), and **chronic** aortic dissection (> 90 days).

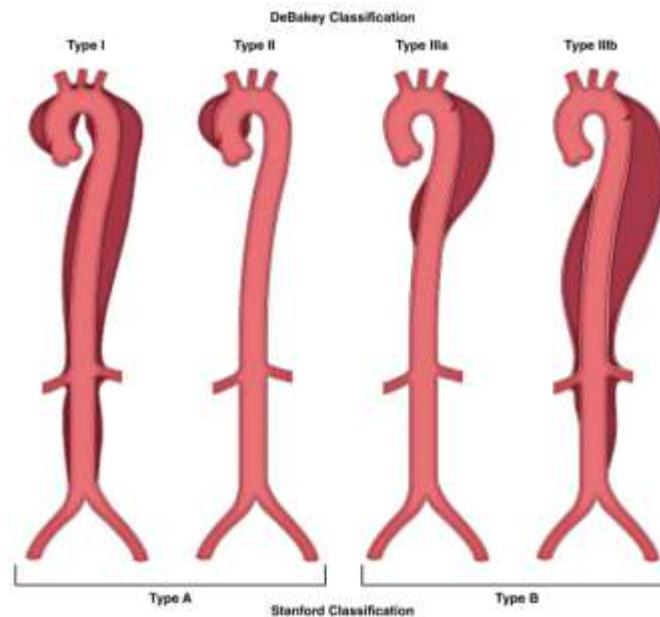


Figure 25-3: DeBakey and Stanford Classification of aortic dissection localization.

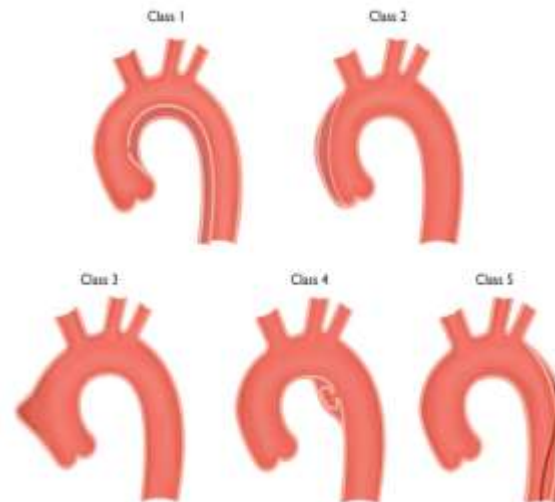


Figure 25-4: Classification of acute aortic syndrome in aortic dissection.

Class 1: Classic AD with true and FL with or without communication between the two lumina. **Class 2:** Intramural haematoma. **Class 3:** Subtle or discrete AD with bulging of the aortic wall. **Class 4:** Ulceration of aortic plaque following plaque rupture. **Class 5:** Iatrogenic or traumatic AD, illustrated by a catheter-induced separation of the intima. **Source:** 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases.

Acute aortic dissection:

▪ **Definition:**

Aortic dissection is defined as disruption of the medial layer provoked by intramural bleeding, resulting in separation of the aortic wall layers and subsequent formation of a true lumen (TL) and a false lumen (FL) with or without communication.

▪ **Causes**

The media of the ascending aorta is rich in elastic fibers. Medial degeneration consists of a loss of elastic fibers and predisposes to ascending aortic aneurysm and dissection.

1. Medial degeneration may be seen with repetitive injury (Hypertension and aging); in fact, the combination of age and Hypertension is responsible for aortic dissection in most patients.
2. More severe medial degeneration, called cystic medial necrosis, may occur in the contexts of bicuspid aortic valve, Marfan syndrome, or coarctation of the aorta.

The aortic wall stress drastically increases with aortic size. Thus, the risk of aortic dissection and progressive aortic dilatation is drastically increased in patients with dilated aorta. However, since a normal-size aorta is much more common than a dilated aorta, only 40% of aortic dissections occur in patients with aortic diameter ≥ 5.5 cm, while 10-20% occur in patients with aortic diameter ≤ 4 cm.

Aortic dissection has traditionally been defined as “acute” during the first 2 weeks after symptom onset and “chronic” when beyond the second week. Investigators from the International Registry of Acute Aortic Dissection (IRAD) proposed that aortic dissection be divided into 4 temporal types: hyperacute (< 24 h), acute (2-7 d), sub-acute (8-30 d), and chronic (> 30 d).

▪ **Mechanisms of aortic dissection:**

- The typical aortic dissection consists of an intimal tear that allows blood to penetrate a diseased medial layer and cleave this media longitudinally. The blood-filled space within the media is the false lumen. Distention of the false lumen with blood may cause the intimal flap to bow into the true lumen and obstruct the lumen or the branches causing ischemia (e.g., carotid, mesenteric, or renal artery). The false lumen may also extend into the branches and cause ischemia.

○ This process is followed either by: Aortic rupture in the case of adventitial disruption **or** Re-entering into the aortic lumen through a second intimal tear which allows the false lumen to decompress and allows blood to flow through it (**Chronic Aortic dissection**). Flow to vital branches supplied by the false lumen is improved, and organ ischemia improves.

▪ **Clinical presentation:** Three clinical features suggest the possibility of aortic dissection:

1. **Predisposing condition:** aortic valve disease, known aortic aneurysm, Marfan, or family history of dissection.
2. **Suggestive symptoms:** chest, back, or abdominal pain that is very abrupt (within seconds), severe, or tearing. Contrary to common belief, the pain of aortic dissection is commonly sharp rather than tearing.
3. **Suggestive signs:** AI murmur (in 25-45%), pulse deficit or blood pressure differential between both arms (~20%), neurologic deficit concomitant to chest pain (5%).

○ The presence of two or three features makes aortic dissection highly probable.

○ In the presence of one feature, the probability is intermediate and aortic imaging is warranted if the patient's symptoms are not clearly explained on chest X-ray or ECG.

○ Up to 5% of aortic dissections have none of these features, but may be suspected by a widened mediastinum on chest X-ray.

Aortic dissection should be suspected in any patient with chest pain and concomitant stroke, mental status changes, or peripheral ischemia.

N.B: Hypotension in a patient with aortic dissection may be:

- Pseudo-hypotension resulting from the obstruction of flow to one limb. Measuring blood pressure in all limbs may unveil this phenomenon.
- True hypotension resulting from tamponade or acute AI. A clinical shock with impaired mental status occurs. Patients with a truly severe hypotension are stabilized with fluid resuscitation and vasopressors if needed, until surgery is performed.

Table 25-7: Clinical data useful to assess the prior probability of acute aortic syndrome:

| High-risk Conditions | High-risk pain features | High-risk examination features |
|--|--|---|
| <ul style="list-style-type: none"> - Marfan syndrome (or other connective tissue disease) - Family history of aortic disease - Known aortic valve disease - Known thoracic aortic aneurysm - Previous aortic manipulation (including cardiac surgeries) | <p>Chest, back or abdominal pain described as any of the following:</p> <ul style="list-style-type: none"> - Abrupt onset - Severe intensity - Ripping or tearing | <ul style="list-style-type: none"> - Evidence of perfusion deficit: <ul style="list-style-type: none"> Pulse deficit Systolic blood pressure difference Focal neurological deficit (in conjugation with pain) - Aortic diastolic murmur (new and with pain) - Hypotension or shock |

Table 25-8: Main clinical presentations and complications of patients with acute aortic dissection:

| | Type A | Type B |
|------------------------------------|------------|------------|
| Chest pain | 80% | 70% |
| Back pain | 40% | 70% |
| Abrupt onset of pain | 85% | 85% |
| Migrating pain | <15% | 20% |
| Aortic regurgitation | 40–75% | N/A |
| Cardiac tamponade | <20% | N/A |
| Myocardial ischaemia or infarction | 10–15% | 10% |
| Heart failure | <10% | <5% |
| Pleural effusion | 15% | 20% |
| Syncope | 15% | <5% |

| | | |
|---|------|------|
| <i>Major neurological deficit (coma/stroke)</i> | <10% | <5% |
| <i>Spinal cord injury</i> | <1% | NR |
| <i>Mesenteric ischaemia</i> | <5% | NR |
| <i>Acute renal failure</i> | <20% | 10% |
| <i>Lower limb ischaemia</i> | <10% | <10% |

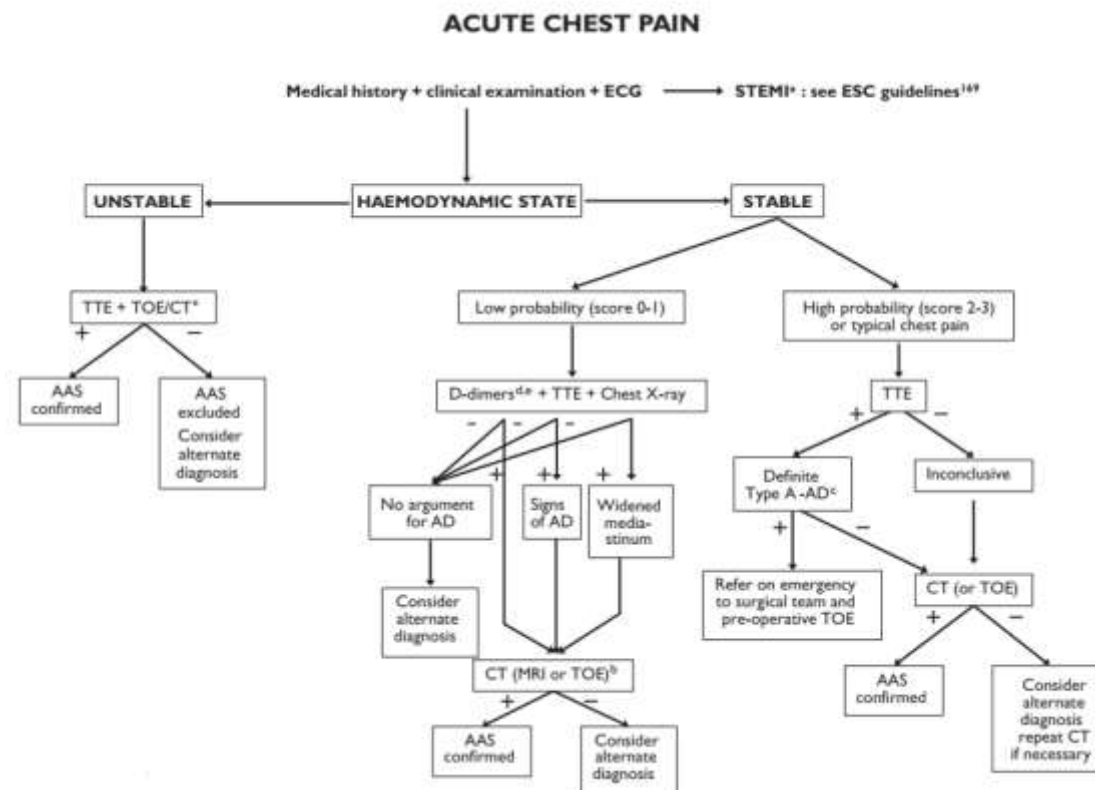


Figure 25-5: Flowchart for decision-making based on pre-test sensitivity of acute aortic syndrome. AAS = acute aortic syndrome; AD = aortic dissection. **A)** STEMI can be associated with AAS in rare cases. **B)** Pending local availability, patient characteristics, and physician experience. **C)** Proof of type-A AD by the presence of flap, aortic regurgitation, and/or pericardial effusion. **D)** Preferably point-of-care, otherwise classical. **E)** Also, troponin to detect NSTEMI. **Source:** 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases.

▪ Complications:

○ **Aortic insufficiency (AI):** Mechanisms include:

- Dissection dilates the sinotubular junction, preventing leaflet coaptation;
 - Dissection extends into the sinotubular junction, where the sinuses of Valsalva insert, resulting in leaflet prolapse and eccentric AI;
 - Dissection flap prolapses through the aortic orifice and prevents leaflet coaptation.
 - AI may also be pre-existent, secondary to a bicuspid aortic valve.
- Aortic rupture into the pericardium, leading to **tamponade**.
 - **Stroke** is seen in 6% of type A aortic dissections. It is due to carotid obstruction by an aortic flap or extension of the dissection into a carotid artery.
 - **STEMI** is seen in 4% of type A aortic dissections. It is easier for the dissection to extend on the outer curve of the aorta into the RCA, explaining why two-thirds of MIs are inferior MIs. MI may be due to the false lumen compressing the coronary ostium or extending into it. In addition, ST depression or T inversion occurs in up to 50% of patients with type A aortic dissection, as a result of demand/supply mismatch or catecholamine-induced ST–T abnormalities. Those ST–T abnormalities may mimic ACS and delay the diagnosis of aortic dissection.
 - Hemorrhagic, large **pleural effusion** may be seen with descending aortic dissection. It results from aortic leakage into the mediastinal pleural space.
 - **Malperfusion syndrome** occurs when there is end-organ ischemia related to inadequate perfusion of the aortic branch vessels. Initially, the true lumen collapses because of the loss of transmural pressure across the dissection flap and the subsequent elastic recoil of the medial smooth muscle. Simultaneously, the false lumen expands immediately because of reduced elastic recoil, depth of the dissection plane within the media, and percentage of the wall circumference involved. Dynamic obstruction occurs when the septum of the dissected intima prolapses across into the ostia of a branch, the ostia itself remains anatomically undamaged. When the dissection tear extends into the vessel proper and creates a stenosis or thrombosis in the artery, static obstruction occurs.

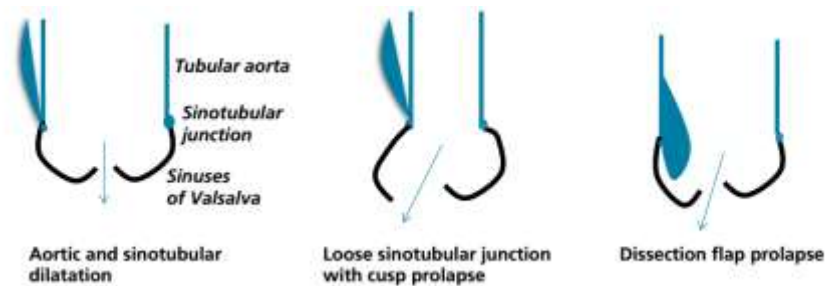


Figure 25-6: Mechanisms of aortic insufficiency (AI) with aortic dissection. Note that the valvular leaflets (cusps) are attached to the *sinuses of Valsalva*. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

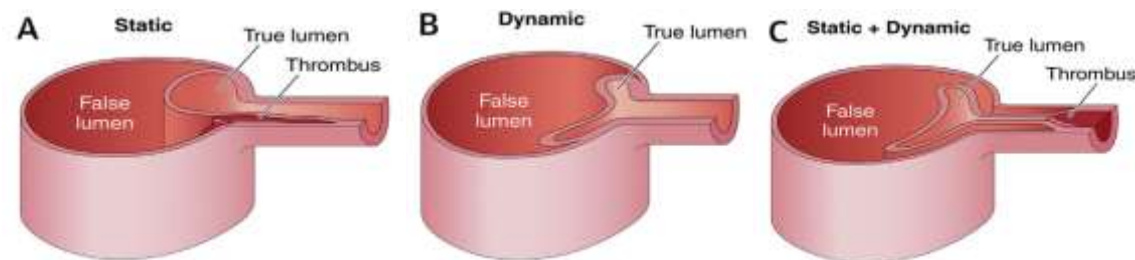


Figure 25-7: (A) Static obstruction occurs when the dissection flap extends from the aortic lumen into the ostium of the affected branch vessel, leading to localized thrombosis of the branch false lumen that narrows or occludes the branch true lumen and, consequently, impairs distal branch perfusion. **(B)** Dynamic obstruction occurs when the false lumen becomes persistently pressurized and compresses the true lumen, in turn pushing the dissection flap up against the ostium of the affected branch vessel, significantly reducing or occluding its flow. **(C)** Sometimes, a branch vessel can suffer from both static and dynamic obstruction at the same time. **Source:** Rodríguez-Palomares JF, et al. Multimodality Assessment of ascending aortic diameters: comparison of different measurement methods. *J Am Soc Echocardiogr.* 2016;29:819–826.e814.

▪ Laboratory testing:

In patients admitted to the hospital with chest pain and suspicion of AD, the following laboratory tests are required for differential diagnosis or detection of complications.

| Table 25-9: Laboratory tests required for patients with acute aortic dissection: | |
|---|--|
| Laboratory tests | To detect signs of: |
| Red blood cell count | <i>Blood loss, bleeding, anaemia</i> |
| White blood cell count | <i>Infection, inflammation (SIRS)</i> |
| C-reactive protein | <i>Inflammatory response</i> |
| ProCalcitonin | <i>Differential diagnosis between SIRS and sepsis</i> |
| Creatine kinase | <i>Reperfusion injury, rhabdomyolysis</i> |
| Troponin I or T | <i>Myocardial ischaemia, myocardial infarction</i> |
| D-dimer | <i>Aortic dissection, pulmonary embolism, thrombosis</i> |
| Creatinine | <i>Renal failure (existing or developing)</i> |
| AST/ALT | <i>Liver ischaemia, liver disease</i> |
| Lactate | <i>Bowel ischaemia, metabolic disorder</i> |
| Glucose | <i>Diabetes mellitus</i> |
| Blood gases | <i>Metabolic disorder, oxygenation</i> |

▪ **Diagnostic imaging:**

- **Chest X-ray:** widening of the aorta and mediastinal silhouette and widening of the aortic knob in 80:90% of patients. The “calcium sign” may be seen (outer displacement of the aortic knob calcium > 1 cm).

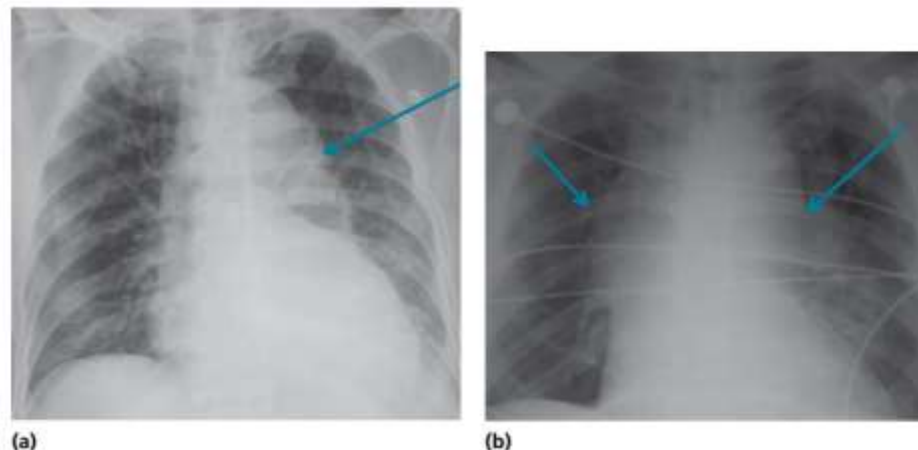


Figure 25-8: (a) Widening of aortic knob (arrow) indicative of descending aortic dissection or aneurysm. (b) Widening of the ascending aortic shadow (right arrow) and the descending aortic knob (left arrow). This patient has ascending and descending aortic dilatation. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

- Perform any of the following three gold-standard studies to establish the diagnosis and type of dissection:
 - CT angiogram.
 - MR angiogram.
 - TOE: This has the additional potential of assessing acute AI and the coronary ostia. It is advantageous if the patient is unstable, because TOE can be performed at the bedside. On a TOE short axis cut:
 - The true lumen is compressed and crescentic, while the false lumen is oval;
 - The false lumen has “smoke” and no flow, or less flow, on Doppler imaging.

Table 25-10: ESC Recommendations on diagnostic work-up of acute aortic syndrome:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|--|-----|---|
| History and clinical assessment: | | |
| <i>In all patients with suspected AAS, pre-test probability assessment is recommended, according to the patient's condition, symptoms, and clinical features.</i> | I | B |
| Laboratory testing: | | |
| <i>In case of suspicion of AAS, the interpretation of biomarkers should always be considered along with the pretest clinical probability.</i> | IIa | C |
| <i>In case of low clinical probability of AAS, negative D dimer levels should be considered as ruling out the diagnosis.</i> | IIa | B |
| <i>In case of intermediate clinical probability of AAS with a positive (point-of-care) D dimer test, further imaging tests should be considered.</i> | IIa | B |
| <i>In patients with high probability (risk score 2 or 3) of AD, testing of D-dimers is not recommended.</i> | III | C |
| Imaging: | | |
| <i>TTE is recommended as an initial imaging investigation.</i> | I | C |
| <i>In unstable patients with a suspicion of AAS, the following imaging modalities are recommended according to local availability and expertise:</i> <ul style="list-style-type: none"> • TOE • CT | I | C |
| <i>In stable patients with a suspicion of AAS, the following imaging modalities are recommended (or should be considered) according to local availability and expertise:</i> <ul style="list-style-type: none"> • CT • MRI • TOE | I | C |
| | I | C |
| | IIa | C |

| | | |
|---|------------|----------|
| <i>In case of initially negative imaging with persistence of suspicion of AAS, repetitive imaging (CT or MRI) is recommended.</i> | I | C |
| <i>Chest X-ray may be considered in cases of low clinical probability of AAS.</i> | IIb | C |
| <i>In case of uncomplicated Type B AD treated medically, repeated imaging (CT or MRI) during the first days is recommended.</i> | I | C |

▪ **Treatment:**

• **Acute Aortic Dissection:**

○ **Medical therapy:**

- Aggressively control blood pressure with β -blockers \pm vasodilators. IV labetalol or the combination of IV esmolol + IV nitroprusside may be used. Morphine may be used for pain control.

β -Blockers reduce the stroke volume and thus reduce the pulse pressure (dP), the slope of aortic pressure rise in systole (dP/dt), and the frequency of aortic exposure to the pulse pressure.

Diltiazem IV may be used if β -blockers are contraindicated.

- **Goal:** Mean BP 60–70 mmHg, SBP < 120 mmHg, heart rate < 60 bpm.

○ **Type A aortic dissection:**

Emergent surgery should be performed and consists of excising the dissected segment of the aorta and interposing a prosthetic graft.

If the sinuses of Valsalva are dilated, the graft needs to extend to the aortic valve.

If moderate or severe AI is present, the aortic valve is repaired (resuspend the leaflets); it may need to be replaced if severe intrinsic valvular disease is present.

○ **Type B aortic dissection:**

- Aggressive blood pressure control is the initial therapy.

- Surgery is indicated for: **(i)** Impending aortic rupture (such as aneurysmal dilatation of the false lumen); **or (ii)** Peripheral ischemia (such as carotid, mesenteric, renal, spinal cord, or lower limb ischemia ⁽¹⁾).
- **Chronic dissection (= dissection that occurred > 2 weeks prior):**
Whether it is type A or B, chronic medical therapy without surgical intervention is the initial treatment of choice at this point. Medical therapy consists of aggressive BP control (SBP < 130 mmHg) with regular monitoring for aneurysm formation and size, extension of the dissection, and development of severe AI. Aneurysmal dilatation of the aorta, particularly the false lumen, occurs frequently and dictates surgery.
- **Prognosis:**
 - Acute aortic dissection of the ascending aorta is highly lethal in symptomatic patients left untreated, with an early mortality of 1% to 2% per hour after symptom onset.
 - Patients with uncomplicated acute type B aortic dissection have a 30-day mortality rate of 10%. However, when patients with acute type B aortic dissection develop complications, such as malperfusion or rupture, the mortality rate increases to 20% by day 2 and to 25% by day 30.
 - In survivors, there is a long-term risk of AI, recurrence of dissection, and secondary aneurysm formation, especially during the first 2 years. This mandates frequent CT/MRI monitoring every 3–6 months for the first 2 years then every 6–12 months afterward.

Intramural hematoma (IMH):

▪ **Definition:**

Aortic IMH describes the presence of blood within the medial layer of the aortic wall in the absence of an overt intimal tear or patent false lumen. The blood may arise from either rupture of the vasa vasorum causing bleeding within the media or small intimal tears not visualized on standard imaging exams.

(1) Surgery is not typically indicated solely for persistent pain (pain being secondary to a distended false lumen).

This entity may account for 10-25% of AAS. The involvement of the ascending aorta, aortic arch and the descending thoracic aorta may account for 30%, 10% and 60% of cases, respectively.

▪ **Diagnosis:**

Intramural hematoma is diagnosed by CT angiograph, MRI, and echocardiography by the presence of a circular or crescent-shaped thickening of > 5 mm of the aortic wall in absence of detectable blood flow.

This can usually be distinguished by CT: the intramural hematoma does not enhance with contrast. Invasive angiography misses IMH, due to the lack of communication between the true and false lumens.

▪ **Predictors of IMH complications:**

- Persistent and recurrent pain despite aggressive medical treatment.
- Difficult blood pressure control.
- Ascending aortic involvement.
- Maximum aortic diameter \geq 50 mm.
- Progressive maximum aortic wall thickness (> 11 mm).
- Enlarging aortic diameter.
- Recurrent pleural effusion.
- Penetrating ulcer or ulcer-like projection secondary to localized dissections in the involved segment.
- Detection of organ ischemia (brain, myocardium, bowels, kidneys, etc).

Penetrating aortic ulcer (PAU):

▪ **Definition:**

PAU is defined as ulceration of an aortic atherosclerotic plaque which leads to a focal disruption in the aortic intima that allows blood to penetrate into the medial layer. Such lesions represent 2–7% of all AAS.

Propagation of the ulcerative process may lead to IMH, pseudoaneurysm, acute AD or even rupture.

PAUs most often appear in the middle or distal descending thoracic aorta, less frequently in the aortic arch and abdominal aorta, and rarely in the ascending aorta.

The natural history of PAU is not well defined, as they can remain stable, enlarge, or progress to either IMH, dissection, pseudoaneurysm, or aortic rupture. CT can distinguish it from typical dissection.

▪ **Management:**

A penetrating ulcer is generally treated conservatively. The treatment is surgical in case of persistent or recurrent pain, transmural extension with pseudoaneurysm, or progressive aneurysmal dilatation.

Aortic pseudoaneurysm:

Aortic pseudoaneurysm (false aneurysm) is defined as a dilation of the aorta due to disruption of all wall layers, which is only contained by the periaortic connective tissue.

In patients with aortic pseudoaneurysms -if feasible and independently of size- interventional or open surgical interventions are always indicated.

(Contained) rupture of aortic aneurysm:

Contained rupture should be suspected in all patients presenting with acute pain, in whom imaging detects aortic aneurysm with preserved integrity of the aortic wall.

Contained rupture of TAA is a condition requiring urgent treatment because, once overt free rupture occurs, most patients do not survive.

Traumatic aortic injury (TAI):

▪ **Definition and epidemiology:**

Blunt traumatic thoracic aortic injury most often occurs as a consequence of sudden deceleration (resulting from head-on or side impact collisions, usually in motor vehicle accidents or falling from a great height). Rapid deceleration results in torsion and

shearing forces at relatively immobile portions of the aorta (such as the aortic root or in proximity of the ligamentum arteriosum or the diaphragm).

A combination of compression and upward thrust of the mediastinum, sudden blood pressure elevation, and stretching of the aorta over the spine may also explain the pathogenesis of TAI.

Accordingly, TAI is located at the aortic isthmus in up to 90% of cases.

Thoracic aortic injury is, after brain injury, the second most common cause of death in blunt trauma patients; the on-site mortality may exceed 80%.

▪ **Classification:**

Type I: Intimal tear, **Type II:** IMH, **Type III:** Pseudoaneurysm, **Type IV:** Rupture.

- **Iatrogenic aortic dissection:** Iatrogenic aortic dissection (IAD) may occur in the setting of:

- Catheter-based coronary procedures.
- Cardiac surgery,
- As a complication of endovascular treatment of aortic coarctation.
- Aortic endografting.
- Peripheral interventions.
- Intra-aortic balloon counterpulsation.
- During transcatheter aortic valve implantation.

Treatment is conservative in most cases, with complete spontaneous healing observed in most instances.

Dissections extending over several centimetres into the ascending aorta or further propagating do require emergency cardiac surgery.

| Table 25-11: ESC Recommendations on management of acute aortic syndrome: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Aortic Dissection, Intramural haematoma And Penetrating aortic ulcer: | | |

| | | |
|---|-----|---|
| <i>In all patients with Type A AD/IMH/PAU, medical therapy including pain relief and blood pressure control is recommended.</i> | I | C |
| <i>In cases of Type A AD/IMH, urgent surgery is indicated.</i> | I | C |
| <i>In the case of Type A PAU, surgery should be considered.</i> | IIa | C |
| <i>In patients with acute Type A AD and organ malperfusion, a hybrid approach (i.e. ascending aorta and/or arch replacement associated with any percutaneous aortic or branch artery procedure) should be considered.</i> | IIa | B |
| <i>In cases of Type B IMH/PAU/AD, initial medical therapy under careful surveillance is recommended.</i> | I | C |
| <i>In complicated Type B AD, TEVAR is recommended.</i> | I | C |
| <i>In complicated Type B IMH/PAU and uncomplicated AD, TEVAR should be considered.</i> | IIa | C |
| <i>In complicated Type B AD/IMH/PAU, surgery may be considered.</i> | IIb | C |
| <i>In uncomplicated Type B IMH/PAU, repetitive imaging (MRI or CT) is indicated.</i> | I | C |
| (Contained) rupture of aortic aneurysm: | | |
| <i>In patients with suspected rupture of the TAA, emergency CT angiography for diagnosis confirmation is recommended.</i> | I | C |
| <i>In patients with acute contained rupture of TAA, urgent repair is recommended.</i> | I | C |
| <i>If the anatomy is favourable and the expertise available, endovascular repair (TEVAR) should be preferred over open surgery.</i> | I | C |
| Traumatic aortic injury: | | |
| <i>In case of suspicion of TAI, CT is recommended.</i> | I | C |
| <i>If CT is not available, TOE should be considered</i> | IIa | C |
| <i>In cases of TAI with suitable anatomy requiring intervention, TEVAR should be preferred to surgery.</i> | IIa | C |

- **Chronic Aortic dissection:**

| Table 25-12: ESC Recommendations for management of chronic aortic Dissection: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Contrast CT or MRI is recommended, to confirm the diagnosis of chronic AD.</i> | I | C |
| <i>Initial close imaging surveillance of patients with chronic AD is indicated, to detect signs of complications as soon as possible.</i> | I | C |
| <i>In asymptomatic patients with chronic dissection of the ascending aorta, elective surgery should be considered.</i> | IIa | C |
| <i>In patients with chronic AD, tight blood pressure control < 130/80 is indicated.</i> | I | C |
| <i>Surgical repair or TEVAR is recommended for complicated Type B AD (aortic diameter > 60 mm, > 10 mm/year growth, malperfusion or recurrent pain).</i> | I | C |

Aortic aneurysms

Aneurysm is the second most frequent disease of the aorta after atherosclerosis. The conventional definition of an arterial aneurysm is any artery that is dilated to at least 1.5 times its expected normal diameter. This definition applies well to the abdominal and descending thoracic aorta. However, it has long been recognized that this definition fails when it comes to defining aneurysms of the aortic root and ascending thoracic aorta. The ascending aorta can be considered “dilated” when it is 4.0 to 4.4 cm and “aneurysm” if it is ≥ 4.5 cm.

While the ascending aorta is richer in elastic fibers than the descending aorta, the descending aorta is much more likely to become heavily atherosclerotic than the ascending aorta. This explains the differences in etiology of ascending vs. descending thoracic aneurysms. **Ascending aortic aneurysm** or dissection is caused by *cystic medial degeneration*, while **descending aortic aneurysm** is caused by *atherosclerosis*. **Arch aneurysms** are related to either medial degeneration or atherosclerosis, and are often an extension of an adjacent ascending or descending aneurysm.

| Table 25-13: ESC Recommendations in patients with aortic aneurysm: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| When an aortic aneurysm is identified at any location, assessment of the entire aorta and aortic valve is recommended at baseline and during follow-up. | I | C |
| In cases of aneurysm of the abdominal aorta, duplex ultrasound for screening of peripheral artery disease and peripheral aneurysms should be considered. | IIa | C |
| Patients with aortic aneurysm are at increased risk of cardiovascular disease: general principles of cardiovascular prevention should be considered. | IIa | C |

Thoracic Aortic Aneurysms:

TAA encompasses a wide range of locations and aetiologies, the most frequent being *degenerative aneurysm of the ascending aorta*. Cystic medial degeneration may result from repetitive aortic injury occurring with age and hypertension, or from connective tissue disorders (e.g., Marfan syndrome), or may be associated with bicuspid aortic valve or a history of aortic coarctation.

Three levels of TAA must be distinguished (sinuses of Valsalva, sinotubular junction, and tubular aorta).

Ascending TAA may involve the sinuses of Valsalva or may be limited to the tubular portion of the aorta as in many elderly hypertensive patients with TAA.

Typically, aortic dilatation associated with bicuspid aortic valve or connective tissue disorders involves both the sinuses and the tubular aorta and may involve the annulus (in the latter case, it is called annuloaortic ectasia).

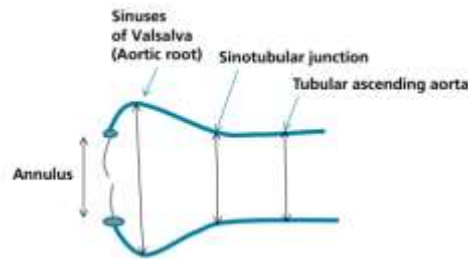


Figure 25-9: Various aortic measurements. The annulus is a stable structure that is part of the ventricle/outflow tract and infrequently dilates, but may dilate in connective tissue disorders (bicuspid aortic valve, Marfan). The aortic diameter at the sinuses of Valsalva level (i.e., the aortic dilatations where the aortic cusps insert, also called aortic root) is normally up to 3.7 cm, while the diameter of the proximal ascending aorta and of the sinotubular junction (junction of the tubular ascending aorta with the sinuses of Valsalva) is normally up to 3.2 cm (must be adjusted for height). Aortic dilatation may occur at the level of the ascending aorta and sinotubular junction (e.g., HTN), or may involve the sinuses of Valsalva.

Aortic dilatation associated with bicuspid aortic valve and cystic medial necrosis (Marfan disease) often involves the sinuses as well as the aorta more distally.

HTN often affects the aorta distal to the sinuses with less effect on the sinuses (e.g., in HTN, the sinotubular junction and distal ascending aorta are dilated with normal diameter at the sinuses).

Source: Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

▪ **Diagnosis:**

- **TTE** provides good images for measurement of the aortic root at the sinuses of Valsalva, sinotubular junction, and early tubular aorta, but may totally miss the mid-ascending aorta.
- **TOE** allows more extensive aortic measurements, but cannot accurately assess the distal ascending aorta and the aortic arch; also, the cut may be oblique rather than central.
- **CT** provides excellent diagnostic value for the whole extent of the aorta. However, axial measurements overestimate the true diameter of the aorta, especially in patients with an elongated, widely curved rather than vertical aorta. Also, axial cuts may miss an aneurysm at the level of the sinuses. Three-dimensional reconstruction overcomes these pitfalls.

Patients with TAA are most often asymptomatic and the diagnosis is made following imaging, performed either for other investigative reasons or for screening purposes. The usefulness of screening patients at risk is well recognized in the case of Marfan syndrome. In patients with a BAV, the value of screening first-degree relatives is more debatable but can be considered.

▪ **Interventions:**

Key decisions regarding management of aortic aneurysms depend on **their size** ⁽¹⁾. *There is a rapid increase in the risk of dissection or rupture when the aortic diameter is > 60 mm for the ascending aorta **and** > 70 mm for the descending aorta.*

• **Interventions on ascending aorta:** There are three forms of TAA repair:

1. If the sinuses are not dilated and the aortic valve is not significantly affected (no moderate or severe AS or AI), the ascending aorta is replaced and the graft sutured proximally at the sinotubular junction.
2. If the sinuses are dilated and the valve has significant regurgitation secondary to the aortic dilatation but is not significantly calcified or fibrotic, the native aorta and sinuses are removed (after freeing the coronary buttons), but the valvular leaflets are left in place and the aortic graft is sutured to the aortic annulus. The coronary buttons are then sutured to the graft (**David or Yacoub procedure**).
3. If the sinuses are dilated and the valve has severe intrinsic abnormality, a composite graft (aorta and aortic valve) is used to replace both the aorta and aortic valve. The coronary buttons are sutured to the aortic graft (**Bentall procedure**), sometimes with the use of interposition graft (**Cabrol procedure**).

Perioperative complications: Mortality (3-5%), MI (5-7%), stroke (2-5%).

• **Interventions on aortic arch aneurysms:**

(1) In adults, aortic diameters are normalized using a ratio of aortic diameter to BSA (known as aortic size index; ASI) or aortic diameter to the patient's height (known as aortic height index; AHI). ASI is a better predictor of adverse aortic events than diameter alone. However, one would not expect a patient's aorta to grow or shrink with significant fluctuations in weight. AHI is at least as well as the ASI and had the advantage of being simpler to calculate. Another approach to normalizing aortic size to height was calculated a ratio of the cross-sectional area of the aorta to the patient's height. The initial studies used a cross-sectional area to height ratio of > 10 cm²/m as a threshold for intervention because of a significant increase in risk of adverse events.

- **In low-risk patients**, classic surgical correction is done; this involves removal of the brachiocephalic arteries en bloc at their common base, followed by replacement of the aortic arch with a graft and reimplantation of the brachiocephalic bloc (deep hypothermic arrest required).
- **In patients with comorbidities**, a stent graft may be positioned in an open antegrade fashion to cover the arch (and the descending aorta if needed), after debranching the brachiocephalic arteries and attaching them to the ascending aorta (**hybrid arch repair**).

Perioperative complications: Mortality (10%) and Stroke (~8–10%).

● **Interventions on descending aortic aneurysms:** Two forms are available for descending TAA:

1. Open replacement of the aorta with a graft: Postoperative mortality is 5-14%
2. Percutaneous endograft placement (stent graft): less invasive with lower postoperative morbidity and mortality and is of particular value in poor surgical candidates.

Both open repair and endograft repair of the descending TAA are associated with a loss of intercostal branches and a risk of spinal cord ischemia and paraplegia. This risk is higher if the repaired aorta is long or if the patient has already had abdominal aortic aneurysm repair.

● **Interventions on aneurysms involving the thoracic aorta:**

In patients with aneurysm involving the ascending aorta, arch, and descending aorta, a complex surgery called **elephant trunk** may be performed (replacement of the ascending aorta and arch, with part of the graft protruding into the descending aorta; this is followed by placement of an endograft in the descending aorta, attached to the protruded graft).

Alternatively, an ascending aortic graft is placed, followed by debranching of the brachiocephalic vessels then endograft placement over the arch and descending aorta.

Table 25-14: ESC Recommendation for interventions on thoracic aortic aneurysm:

Recommendations

Class Level

Interventions on ascending aorta:

| | | |
|--|------------|----------|
| <i>Surgery is indicated in patients who have aortic root aneurysm, with maximal aortic diameter ≥ 50 mm for patients with Marfan syndrome ⁽¹⁾.</i> | I | C |
| <i>Surgery should be considered in patients who have aortic root aneurysm, with maximal ascending aortic diameters:</i> <ul style="list-style-type: none"> <i>≥ 45 mm for patients with Marfan syndrome with risk factors ⁽²⁾.</i> <i>≥ 50 mm for patients with bicuspid valve with risk factors ⁽³⁾.</i> <i>≥ 55 mm for other patients with no elastopathy ⁽⁴⁾.</i> | IIa | C |
| <i>Lower thresholds for intervention may be considered according to body surface area in patients of small stature or in the case of rapid progression, aortic valve regurgitation, planned pregnancy, and patient's preference.</i> | IIb | C |
| Interventions on aortic arch aneurysms: | | |
| <i>Surgery should be considered in patients who have isolated aortic arch aneurysm with maximal diameter ≥ 55 mm.</i> | IIa | C |
| <i>Aortic arch repair may be considered in patients with aortic arch aneurysm who already have an indication for surgery of an adjacent aneurysm located in the ascending or descending aorta.</i> | IIb | C |
| Interventions on descending aortic aneurysms: | | |
| <i>TEVAR should be considered, rather than surgery, when anatomy is suitable.</i> | IIa | C |

(1) Decision should also take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.

(2) Risk factors: **(A)** Family history of AD **(B)** Aortic size increase > 3 mm/year (on repeated measurements using the same imaging technique, at the same aorta level, with side-by-side comparison and confirmed by another technique), **(C)** Severe aortic or mitral regurgitation, or **(D)** Desire for pregnancy.

(3) Risk factors: **(A)** Coarctation of the aorta, **(B)** Systemic hypertension, **(C)** Family history of dissection, or **(D)** Increase in aortic diameter > 3 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level, with side-by-side comparison and confirmed by another technique).

(4) For patients with LDS or vascular type IV Ehlers-Danlos syndrome (EDS), lower thresholds should be considered, possibly even lower than in Marfan syndrome.

| | | |
|--|------------|----------|
| <i>TEVAR should be considered in patients who have descending aortic aneurysm with maximal diameter ≥ 55 mm.</i> | Ila | C |
| <i>When TEVAR is not technically possible, surgery should be considered in patients who have descending aortic aneurysm with maximal diameter ≥ 60 mm.</i> | Ila | C |
| <i>When intervention is indicated, in cases of Marfan syndrome or other elastopathies, surgery should be indicated rather than TEVAR.</i> | Ila | C |
| Follow-up after endovascular treatment for aortic diseases: | | |
| <i>After TEVAR or EVAR, surveillance is recommended after 1 month, 6 months, 12 months, and then yearly. Shorter intervals can be proposed in the event of abnormal findings requiring closer surveillance.</i> | I | C |
| <i>CT is recommended as the first-choice imaging technique for follow up after TEVAR or EVAR.</i> | I | C |
| <i>For follow-up after (T)EVAR in young patients, MRI should be preferred to CT for magnetic resonance compatible stent grafts, to reduce radiation exposure.</i> | Ila | C |
| <i>For patients with TAA < 45 mm, annual imaging is recommended; while in patients with TAA 45 mm and < 55 mm, imaging every 6 months is recommended, unless the stability of the lesions is confirmed by serial imaging.</i> | I | C |

Abdominal Aortic Aneurysm:

▪ Definition:

While an aneurysm is generally defined as arterial enlargement with loss of arterial wall parallelism, AAA is usually defined as a diameter ≥ 30 mm. AAA is almost exclusively infrarenal, but may extend above the renal arteries and may be thoracoabdominal.

The main aetiology of this disease is degenerative, although it is frequently associated with atherosclerotic disease.

▪ Risk Factors:

Age, male gender, personal history of atherosclerotic cardiovascular disease, smoking and hypertension are all associated with the presence of AAA.

Dyslipidaemia is considered as a weaker risk factor while, in contrast, diabetic patients are at decreased risk for AAA.

Family history of AAA is a powerful predictor of prevalent AAA (AAA occurs in up to 30% of siblings of patients with AAA).

▪ **Natural history:**

Large and life-threatening AAA is preceded by a long period of subclinical growth in the diameter of the aneurysm, estimated at < 1-6 mm/year.

The risk of rupture rises exponentially with the aneurysm's maximal diameter and is higher in women than in men at similar diameters; women present ruptured AAA on average 10 mm smaller than men.

▪ **Screening:**

Ultrasound is the best screening tool, but CT generally provides more accurate sizing and better defines the extent of AAA and its relation with branch vessels (e.g., renal arteries).

| Table 25-15: ESC Recommendations for AAA screening: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Population screening for AAA with ultrasound: | | |
| - is recommended in all men > 65 years of age. | I | A |
| - may be considered in women > 65 years of age with history of current/past smoking. | IIb | C |
| - is not recommended in female nonsmokers without familial history. | III | C |
| Targeted screening for AAA with ultrasound should be considered in first-degree siblings of a patient with AAA. | IIa | B |
| Opportunistic screening for AAA during TTE: | | |
| - should be considered in all men > 65 years of age. | IIa | B |
| - may be considered in women > 65 years with a history of current/past smoking. | IIb | C |

N.B:

Approximately 10% of patients with AAA have popliteal aneurysms, usually bilateral aneurysms, which should always be sought. On the other hand, ~40% of patients with popliteal aneurysms have AAA.

The main risks of popliteal aneurysms are thrombosis, embolization, and limb ischemia rather than rupture.

▪ **Management:**

- **Surgical treatment** consists of opening the aneurysm longitudinally with clot removal, followed by transecting the aneurysmal pocket proximally and distally, then suturing a graft proximally and distally to the iliac arteries. The open aneurysmal sac is left in place and wrapped around the graft for support and protection from the bowels.

Surgical mortality is ~5% in elective cases (2% in low-risk); ~50% in emergent cases of aortic rupture.

Common and internal iliac aneurysms are rarely isolated and frequently accompany AAA (up to 40% of AAAs). The aneurysm is treated when it exceeds 3-3.5 cm in diameter.

A popliteal aneurysm is treated when it exceeds 2 cm, preferably before limb ischemia occurs; when the latter occurs, the risk of limb loss is high.

- **Percutaneous endovascular aortic repair (EVAR):**

- EVAR involves graft stent placement at the level of the aneurysm, excluding the AAA from the circulation.
- The endograft is a bifurcating endograft that covers the aorta and both iliacs. It has two parts: **(i)** a body and a right limb landing into the right iliac (deployed through a right femoral access), and **(ii)** a left limb landing into the left iliac (deployed through a left femoral access).
- **The technical requirements for EVAR are: (1)** at least 1.5 cm of normal aorta (diameter < 3 cm) between the renal arteries and the AAA to allow proximal anchoring of the device, **(2)** minimal angulation of the AAA, **(3)** patency of the superior mesenteric/celiac side branches (as the inferior mesenteric branch is covered by the endograft), and **(4)** patent distal iliac vessels ≥ 7 mm in diameter.

- EVAR leads to a lower perioperative mortality than open repair (1.8% vs. 4.3% as shown in EVAR-1 and DREAM trials), but a higher late mortality (particularly in case of AAA > 6.5 cm due to inappropriate seal and inability to fully exclude AAA). There is a slightly higher risk of graft rupture with EVAR (up to 2% per year), and a significantly higher need for reinterventions for endoleaks (~20-30% at 6 years).
- Endoleaks frequently occur. An endoleak means that the aneurysm is not fully excluded from the circulation; it is identified by a persistent flow of contrast into the aneurysm. Because of endoleaks, endovascular repair is mainly indicated for patients at intermediate or high operative risk.

Types of endoleaks:

- **Type 1:** Poor sealing at the proximal or distal end of the graft.
- **Type 2:** Retrograde endoleak from collateral flow. Leak from lumbar, inferior mesenteric, or internal iliac artery that are covered by the endograft but receive retrograde flow through collaterals ⁽¹⁾.
- **Type 3:** Fabric tear or stent frame fracture or separation.

Types 1 and 3 endoleaks have, however, been recently reduced with the newer generation of devices.

In patients unsuitable for open repair, EVAR is performed, but in those high-risk patients even EVAR has a high early mortality (8%) and most patients die from comorbidities within 5 years, without a clear benefit of EVAR in terms of overall survival (EVAR-2 trial).

Table 25-16: ESC Recommendations on the management of patients with enlarged aorta or AAA:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Asymptomatic patients: | | |
| <i>In patients with abdominal aortic diameter of 25-29 mm, new ultrasound imaging should be considered 4 years later.</i> | IIa | B |

(1) Type 2 endoleak may be followed with serial CT scans and treated selectively if the aneurysmal sac grows.

| | | |
|--|------------|----------|
| <i>Surveillance is indicated and safe in patients with AAA with a maximum diameter of < 55 mm and slow (< 10 mm/year) growth ⁽¹⁾.</i> | I | A |
| <i>In patients with small (30-55 mm) AAAs, the following time interval for imaging should be considered:</i> <ul style="list-style-type: none"> - every 3 years for AAA of 30–39 mm diameter. - every 2 years for AAA of 40–44 mm diameter. - every year for AAA > 45 mm diameter ⁽²⁾. | IIa | B |
| <i>Smoking cessation is recommended to slow growth of the AAA.</i> | I | B |
| <i>To reduce aortic complications in patients with small AAAs, the use of statins and ACE-inhibitors may be considered.</i> | IIb | B |
| <i>AAA repair is indicated if:</i> <ul style="list-style-type: none"> • AAA diameter exceeds 55 mm. ⁽³⁾ • Aneurysm growth exceeds 10 mm/year. | I | B |
| <i>If a large aneurysm is anatomically suitable for EVAR, either open or endovascular aortic repair is recommended in patients with acceptable surgical risk.</i> | I | A |
| <i>If a large aneurysm is anatomically unsuitable for EVAR, open aortic repair is recommended.</i> | I | C |
| <i>In patients with asymptomatic AAA who are unfit for open repair, EVAR, along with best medical treatment, may be considered ⁽⁴⁾.</i> | IIb | B |
| Symptomatic patient: | | |

(1) With < 1% risk of rupture between two AAA imaging assessments.

(2) This interval may be shortened in women or in the case of rapid growth between previous assessments.

(3) Individual decision for operative aneurysm correction should also be influenced by the patient's gender. At a given size, AAAs in women are up to four times as likely to rupture under surveillance, thus aortic repair can be discussed at a lower threshold of probably 50 mm. The patient's life expectancy should also be considered prior to decision for intervention.

(4) Since only aneurysm-related and not all-cause mortality is improved, informed patient choice is to be taken into account.

| | | |
|--|------------|----------|
| <i>In patients with suspected rupture of AAA, immediate abdominal ultrasound or CT is recommended.</i> | I | C |
| <i>In case of ruptured AAA, emergency repair is indicated.</i> | I | C |
| <i>In case of symptomatic but non ruptured AAA, urgent repair is indicated.</i> | I | C |
| <i>In case of symptomatic AAA anatomically suitable for EVAR, either open or endovascular aortic repair is recommended.</i> | I | A |
| Follow-up after endovascular treatment for aortic diseases: | | |
| <i>After TEVAR or EVAR, surveillance is recommended after 1 month, 6 months, 12 months, and then yearly. Shorter intervals can be proposed in the event of abnormal findings requiring closer surveillance.</i> | I | C |
| <i>CT is recommended as the first-choice imaging technique for follow up after TEVAR or EVAR.</i> | I | C |
| <i>For follow-up after (T)EVAR in young patients, MRI should be preferred to CT for magnetic resonance compatible stent grafts, to reduce radiation exposure.</i> | IIa | C |
| <i>If neither endoleak nor AAA sac enlargement is documented during first year after EVAR, then colour Doppler US, with or without contrast agents, should be considered for annual post operative surveillance, with non contrast CT imaging every 5 years.</i> | IIa | C |
| <i>Long-term surveillance of open abdominal aortic repair may be considered at loose (5-year) intervals using colour DUS or CT imaging.</i> | IIb | C |

Genetic diseases affecting the aorta

Genetic diseases affecting the aorta are broadly split into two categories: syndromic and non-syndromic, both essentially displaying **autosomal dominant** transmission.

▪ Genetic testing in aortic diseases

| Table 25-17: ESC Recommendations for genetic testing in aortic diseases: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended to investigate first-degree relatives (siblings and parents) of a subject with thoracic aortic aneurysms and dissection (TAAD) to identify a familial form in which relatives all have a 50% chance of carrying the family mutation/disease.</i> | I | C |
| <i>Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing.</i> | I | C |
| <i>Variability of age of onset warrants screening every 5 years of 'healthy' at-risk relatives until diagnosis (clinical or molecular) is established or ruled out.</i> | I | C |
| <i>In familial non-syndromic TAAD, screening for aneurysm should be considered, not only in the thoracic aorta, but also throughout the arterial tree (including cerebral arteries).</i> | Ila | C |

Non-syndromic familial TAADs:

Most patients with TAAD do not have a known genetic syndrome. In these patients, familial aggregation with an affected first-degree relative is found in up to 19% of cases.

These non-syndromic forms of TAAD (nsTAAD) may be associated with BAV and/or persistent ductus arteriosus, and display typical cystic medial necrosis on pathological examination.

Non-syndromic TAAD presents an **autosomal dominant** transmission with great clinical variability (notably in women) and decreased penetrance.

Inherited syndromic TAAD:

▪ **Marfan syndrome:**

- Marfan syndrome is an **autosomal dominant**, age-related (that is, progressing with age) genetic disorder of the connective tissue with prominent manifestations in the skeletal, ocular and cardiovascular systems. It is the most frequent heritable connective tissue disorder.
- Marfan syndrome is essentially associated with mutations in the **FBN1 gene** that encodes **fibrillin-1**, a major structural component of the extracellular matrix that provides support to connective tissues, particularly in arteries, the perichondrium and structures in the eye.
- Up to 25% of FBN1 pathogenetic variants are de novo (the mutation is new in the affected individual).
- The diagnosis of Marfan syndrome is based on the **Ghent II criteria**. Requirement for the diagnosis of Marfan syndrome according to Ghent II criteria are:
 - 1) Aortic root dilatation **and** (ectopia lentis or FBN1 mutation or systemic score of ≥ 7 ⁽¹⁾).
 - 2) Ectopia lentis with a FBN1 mutation known to cause ascending aorta dilatation
 - 3) Family history of Marfan syndrome and (ectopia lentis or aortic root dilatation or systemic score of ≥ 7).

(1) **Systemic score:**

- **3 points**= wrist **and** thumb sign.
- **2 points**= pectus carinatum deformity, hindfoot deformity, spontaneous pneumothorax, dural ectasia, protutio acetabulae.
- **1 point**= wrist or thumb sign, pectus excavatum or chest asymmetry, plain flat foot, scoliosis or thoracolumbar kyphosis, reduced elbow extension, three or five facial features, skin striae, severe myopia, mitral valve prolapse.

- **Management** requires medical therapy to slow the rate of growth of aneurysms and decrease the risk of dissection. Both β -blockers and ARBs together are used to lessen haemodynamic stress on the aortic wall and potentially affect signalling pathways implicated in the pathogenesis of disease.
Surgery is indicated in patients who have aortic root disease with a maximal aortic sinus diameter ≥ 50 mm or ≥ 45 mm with additional risk factors (Family history of aortic dissection at a low diameter, progressive AR, desire for pregnancy, uncontrolled hypertension, and/or aortic size increase > 3 mm/year).
- Routine surveillance with imaging techniques such as TTE, CT or MRI is necessary to monitor aneurysm growth and determine when to perform prophylactic repair surgery to prevent aortic dissection.

▪ **Turner syndrome (TS):**

- TS is essentially caused by partial or complete monosomy of the X chromosome (karyotype 45X0).
- **Diagnosis:** (based on clinical findings and cytogenetic analyses).
 - Affected women display short stature, various congenital cardiac defects (particularly, coarctation of the aorta and Bicuspid aortic valve), and metabolic and hormonal alterations leading to obesity, impaired glucose tolerance, hyperlipidaemia, and ovarian failure.
 - Hypertension and brachiofemoral delay due to coarctation of the aorta, usually identified in childhood.
 - A generalized dilation of major vessels is observed, notably the aorta, the brachial, and carotid arteries.
 - Elongation of the transverse arch and aortic dilation (typically at the root of the ascending aorta) are observed in 30% of cases.
 - The incidence of AD in women with TS is 100 times as great as for women in general, occurring in the third and fourth decades of life.
- **Management:** The management of adult women with TS associates imaging (echocardiogram and thoracic MRI) with cardiovascular risk assessment. Elective surgery for ascending aorta aneurysms should be considered in women with Turner

syndrome who are > 16 years of age, and have an ascending aortic size index > 25 mm/m², if associated with risk factors for aortic dissection (elongation of the transverse aorta, CoA, and/or hypertension).

- **Follow-up** will be related to risk categories (absence or number of standard cardiovascular risk factors): TTE every 3-5 years for low risk, thoracic MRI every 3-5 years for moderate risk, and referral to a cardiologist with 1-2-yearly thoracic MRI for high-risk patients.

▪ **Ehlers-Danlos syndrome (Vascular type):**

- Ehlers Danlos syndrome (EDS) is a group of hereditary connective tissue disorders that manifests clinically with skin hyperelasticity, hypermobility of joints, atrophic scarring, and fragility of blood vessels. In 2017, a new international classification of EDS was proposed with 13 different variants (including the vascular EDS and cardiac valvular EDS).
- Vascular EDS involves an **autosomal dominant** inheritance pattern and is associated with mutations in the **COL3A1** and/or **COL1A1** genes, which code for type III and type I **collagen**, respectively.
- **Diagnosis:**
 - Major clinical criteria:** arterial rupture at a young age (Arteries can dissect without previous dilation and are thus unpredictable), uterine rupture (specifically 3rd trimester with no risk factors), the formation of a carotid-cavernous sinus fistula without trauma, and a family history confirmed via genetic testing.
 - Minor criteria:** Congenital hip dislocation and spontaneous pneumothorax.
- **Prognosis:** Individuals with vascular EDS have significantly shortened life spans (50% mortality rate by 48 years) due to the spontaneous rupture of visceral organs (colon, uterus) and blood vessels; it affects the entire vascular system and the heart.
- **Management:** Non-invasive imaging is the preferred approach for evaluating vascular alterations; surgery is only contemplated in potentially fatal complications, since the fragility of tissue, haemorrhagic tendency, and poor wound healing confer an added surgical risk. Prolonged post-operative monitoring is required.

N.B: Cardiac-valvular EDS involves an **autosomal recessive** inheritance pattern and is associated with mutations in the COL1A2 and/or NMD genes, which code for type I collagen.

Major criteria include: skin hyperextensibility, atrophic scarring, easy bruisability, restricted or generalized joint hypermobility, and progressive cardiac-valvular problems.

Minor criteria include: foot deformities, pectus deformity, joint dislocations, and inguinal hernias.

▪ **Loeys-Dietz syndrome (LDS):**

First described in 2005, LDS is an **autosomal dominant** connective tissue disorder that arises from mutations altering the transforming growth factor β (**TGF- β**) signalling pathway.

It is combined of the triad of: **(1)** Arterial tortuosity and aneurysms throughout the arterial tree, **(2)** Ocular hypertelorism (increased distance between the eyes), and **(3)** High arches palate with bifid uvula.

▪ **Aneurysms-osteoarthritis syndrome (AOS):**

- AOS is a new syndromic TAAD that accounts for approximately 2% of familial TAAD. This **autosomal dominant** condition associated with mutations in the **SMAD3 gene**, which encodes an intracellular effector of **TGF- β** signalling.
- It combines early-onset joint abnormalities (including osteoarthritis and osteochondritis dissecans) and aortic aneurysms and dissections. Mild craniofacial-, skin-, and skeletal features may also be found, overlapping with Marfan syndrome and LDS.
- There is no current consensus on management. Beta-blockade may be beneficial in AOS, since it displays identical aortic alterations to those observed in Marfan syndrome and Loeys-Dietz syndrome, for which this treatment is efficient.

▪ **Arterial tortuosity syndrome (ATS):**

- ATS is a very rare **autosomal recessive** disease, caused by mutations in **SLC2A10**.
- It is characterized by arterial tortuosity, elongation, stenosis, and aneurysm of the large- and middle-sized arteries.

- **Complications** include: early and aggressive aortic root aneurysms, neonatal intracranial bleeding, ischemic stroke, and gastric perforation.
- **Management** of these patients requires a baseline whole-body vascular imaging, and follow-up should be individually tailored, based on the rate of enlargement of vascular diameters and the family history.

| Table 25-18: ESC Recommendations for aortic surgery in aortopathies: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Marfan syndrome and HTAD: | | |
| <i>Aortic valve repair, using the reimplantation or remodelling with aortic annuloplasty technique, is recommended in young patients with Marfan syndrome or related HTAD with aortic root dilation and tricuspid aortic valves, when performed by experienced surgeons.</i> | I | C |
| <i>Surgery is indicated in patients with Marfan syndrome who have aortic root disease with a maximal aortic sinus diameter ≥ 50 mm. ⁽¹⁾</i> | I | C |
| <i>Surgery should be considered in patients with Marfan syndrome who have aortic root disease with maximal aortic sinus diameter ≥ 45 mm and additional risk factors ⁽²⁾.</i> | IIa | C |
| <i>Surgery should be considered in patients with a TGFBR1 or TGFBR2 mutation (including LoeysDietz syndrome) who have aortic root disease with maximal aortic sinus diameter ≥ 45 mm.</i> | IIa | C |
| Turner syndrome: | | |
| <i>In women with Turner syndrome who are > 16 years of age, and have an ascending aortic size index > 25 mm/m², Elective surgery for ascending aorta aneurysms:</i> | | |
| | IIa | C |

(1) At the extreme ends of the BSA range, recommended cut-offs may require appropriate adjustment.

(2) Family history of aortic dissection at a low diameter (or personal history of spontaneous vascular dissection), progressive AR, desire for pregnancy, uncontrolled hypertension, and/or aortic size increase > 3 mm/year (on repeated measurements using the same ECG-gated imaging technique measured at the same level of the aorta with comparison and confirmed by another technique).

- *should be considered if associated with risk factors for aortic dissection* ⁽¹⁾.
- *may be considered even if no associated risk factors for aortic dissection.*

IIb

C

Aortic diseases associated with bicuspid aortic valve:

○ Epidemiology and associations:

- Bicuspid aortic valve is the most common congenital cardiac defect, with a prevalence at birth of 1-2%. Males are more often affected than females, with the ratio ranging from 2:1 to 4:1.
- It is present in > 50% of patients with aortic coarctation and in ~10% of women with Turner syndrome.
- It has a familial trend (36% have first-degree relative affected). Screening of the patient's children is appropriate.
- BAV is the result of fusion of the RCC with LCC in > 70% of patients, of fusion of the RCC with NCC in 10-20%, and due to fusion of LCC with NCC in 5-10%.

○ Pathophysiology: **Notch1 gene** mutations are associated with BAV.

- BAV associated with aortic dilatation: Aortic dilatation (defined as an aorta diameter of > 40 mm irrespective of body surface area, or of > 27.5 mm/m² for people of short stature) occurs in 50-60% of patients with BAV by the age of 30. This aortopathy is mainly secondary to cystic medial necrosis and is partly exaggerated by AS's post-stenotic dilatation or AI's volume and pressure load.

Various subtypes of BAV are associated with different forms of aortic dilation:

In LCC-RCC type BAV, ascending aorta dilation is common, but aortic root dilation is also seen.

In the RCC-NCC type, the aortic root is rarely affected and only dilation of the ascending aorta is seen.

Only the LCC-RCC type of BAV is associated with aortic coarctation.

(1) *elongation of the transverse aorta, CoA, and/or hypertension*

- BAV as a cause of AS: The presence of two rather than three leaflets leads to a smaller surface in contact with the high-pressure stroke volume and marked leaflet bending, making the BAV more susceptible to shear stress. Progressive stress leads to calcific degeneration and AS later in life. The more asymmetrical the cusps are, the higher the stress is, and the faster AS develops.
- BAV as a cause of AI: In early adult life (age of 20-50 years), 20% of BAV develop AI. AI may be related to: dilated aortic root, prolapse of the asymmetrically large cusp (can't support the extra weight of blood in diastole), myxoid degeneration with malcoaptation, endocarditis, or retraction of a fibrotic/calcified leaflet.

- **Screening in relatives:**

Because of BAV's strong familial association, screening of first-degree relatives may be considered.

- **Follow-up:**

In cases of an increase in diameter > 3 mm/year or a diameter > 45 mm measured on TTE, a measurement with another imaging modality (MRI or CT) is indicated.

From a diameter of 45 mm, annual follow-up of the ascending aorta is advised.

If TTE cannot reliably visualize the ascending aorta, annual MRI (or CT if MRI is not possible) is indicated.

- **Prognosis:**

The risk of dissection and rupture increases with the diameter of the aorta, with a sharp increase at a diameter of 60 mm.

When treated according to guidelines, the prognosis is favourable -much better than that of Marfan syndrome- and similar to that of an age-matched normal population.

- **Management:**

| Table 25-19: ESC Recommendations for Management of aortic root dilation in patients with BAV: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Initial Evaluation and follow up: | | |
| <i>Patients with known BAV should undergo an initial TTE to assess the diameters of the aortic root and ascending aorta.</i> | I | C |

| | | |
|---|-----|---|
| <i>Cardiac MRI or CT is indicated in patients with BAV when the morphology of the aortic root and the ascending aorta cannot be accurately assessed by TTE.</i> | I | C |
| <i>Serial measurement of the aortic root and ascending aorta is indicated in every patient with BAV, with an interval depending on aortic size, increase in size and family history</i> | I | C |
| <i>In the case of a diameter of the aortic root or the ascending aorta > 45 mm or an increase > 3 mm/year measured by echocardiography, annual measurement of aortic diameter is indicated.</i> | I | C |
| <i>In the case of aortic diameter > 50 mm or an increase > 3 mm/year measured by echocardiography, confirmation of the measurement is indicated, using another imaging modality (CT or MRI).</i> | I | C |
| Management: | | |
| <i>In cases of BAV, surgery of the ascending aorta is indicated in case of:</i> <ul style="list-style-type: none"> - Aortic root or ascending aortic diameter > 55 mm. - Aortic root or ascending aortic diameter > 50 mm in the presence of other risk factors. - Aortic root or ascending aortic diameter > 45 mm when surgical AVR is scheduled. | I | C |
| <i>Beta-blockers may be considered in patients with BAV and dilated aortic root > 40 mm.</i> | IIb | C |
| <i>In patients with any elastopathy or BAV with dilated aortic root (> 40 mm), isometric exercise with a high static load (e.g. weightlifting) is not indicated and should be discouraged.</i> | III | C |
| Screening: | | |
| <i>Because of familial occurrence, screening of first-degree relatives should be considered.</i> | IIa | C |

Coarctation of the aorta:

For more details, see Congenital heart diseases

| Table 25-20: ESC Recommendations for intervention in coarctation of the aorta: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Repair of coarctation or re-coarctation (surgically or catheter based) is indicated in hypertensive patients with an increased non-invasive gradient between upper and lower limbs confirmed with invasive measurement (peak-to-peak ≥ 20 mmHg) with preference for catheter treatment (stenting), when technically feasible. | I | C |
| Catheter treatment (stenting) should be considered in hypertensive patients ⁽¹⁾ with $\geq 50\%$ narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is < 20 mmHg, when technically feasible. | IIa | C |
| Catheter treatment (stenting) should be considered in normotensive patients with an increased non-invasive gradient confirmed with invasive measurement (peak-to-peak ≥ 20 mmHg), when technically feasible | IIa | C |
| Catheter treatment (stenting) may be considered in normotensive patients with $\geq 50\%$ narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is < 20 mmHg, when technically feasible. | IIb | C |

Atherosclerotic lesions of the aorta

(1) Right arm ambulatory blood pressure monitoring should be considered for the diagnosis of hypertension.

Thromboembolic aortic disease:

- As a result of the atherosclerotic process, aortic plaques consist of the accumulation of lipids in the intima-media layer of the aorta.
- Secondary inflammation, fibrous tissue deposition, and surface erosions with subsequent appearance of thrombus may cause either thrombotic (thromboembolic) or atherosclerotic (cholesterol crystal) embolism:

Thromboemboli are usually large, and commonly occlude medium-to-large arteries, causing stroke, transient ischaemic attack, renal infarct, and peripheral thromboembolism.

Cholesterol crystal emboli tend to occlude small arteries and arterioles, and may cause the 'blue-toe' syndrome, new or worsening renal insufficiency, and mesenteric ischaemia.

Table 25-21: ESC Recommendation on Management of aortic plaque:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In the presence of aortic atherosclerosis, general preventive measures to control risk factors are indicated.</i> | I | C |
| <i>In the case of aortic plaque detected during the diagnostic work-up after stroke or peripheral embolism, anticoagulation or antiplatelet therapy should be considered. The choice between the two strategies depends on comorbidities and other indications for these treatments.</i> | IIa | C |
| <i>Prophylactic surgery to remove high-risk aortic plaque is not recommended.</i> | III | C |

Mobile aortic thrombosis:

Mobile thrombi in the aorta of young patients without diffuse atherosclerosis have been reported since the regular use of TOE in patients with cerebral or peripheral emboli, mostly located at the aortic arch.

The pathophysiology of these lesions is unclear.

Medical treatment (heparinization), endovascular stenting, or surgery have been proposed.

Atherosclerotic aortic occlusion:

Abdominal aortic occlusion is rare and results in a major threat of leg amputation or death. Extensive collateralization usually prevents the manifestation of acute ischaemic phenomena. Aortic occlusion can also be precipitated by hypercoagulable states. The diagnosis is mostly made with the use of Doppler ultrasonography. Treatment may be bypass grafting or aorto-iliac endarterectomy. Endovascular therapy has also been proposed.

Calcified aorta:

Calcification occurs in the **media**, and the amount of calcification is directly associated with the extent of atherosclerosis. The presence of severe atherosclerosis of the aorta causes an eggshell-like appearance visualized on chest X-ray (porcelain aorta). In patients requiring CABG and aortic valve replacement with porcelain aorta, Off-pump coronary bypass and transcatheter aortic valves implantation (TAVI) may render a solution.

Coral reef aorta:

‘Coral reef’ aorta is a very rare calcifying stenotic disease of the juxta renal and suprarenal aorta.

Coral reef aorta is described as rock-hard calcifications in the visceral part of the aorta. These heavily calcified plaques grow into the lumen and can cause significant stenosis, which may develop into bowel ischaemia, renal failure, or hypertension due to renal ischaemia.

Vascular surgery was used in the past but, recently, endovascular interventions play a greater role, particularly in high-risk individuals with multiple comorbidities.

Aortitis

Aortitis is the general term used to define inflammation of the aortic wall. Aortitis can be due to inflammatory (more common) or infectious causes:

- The inflammatory causes of aortitis include:
 - Inflammatory vasculitis, namely giant cell/temporal arteritis and Takayasu arteritis.
 - Other inflammatory conditions such as Behcet's disease, Buerger disease, Kawasaki disease, ankylosing spondylarthritis, and Reiter's syndrome.
- Infections due to Staphylococcus, Salmonella, and mycobacteria have been reported to cause infective aortic disease, supplanting the infection by Treponema pallidum in the past.

Giant cell arteritis (GCA):

- Giant cell arteritis (GCA) is a granulomatous large vessel vasculitis that preferentially involves the cranial arteries, aorta and its proximal branches (especially in the upper extremities). When the aorta is affected, it may result in thoracic aortic aneurysm.
- GCA is the most common systemic vasculitis in adults. It tends to affect the older population (almost exclusively in patients over age 50), more in women than in men.
- The initial symptoms of GCA may be vague, such as malaise, fever, and night sweats. Features of vascular involvement include headache, scalp tenderness, and jaw claudication (cramping pain in the jaw while chewing). A less common but serious feature is partial or complete loss of vision affecting one or both eyes. Some patients suddenly go completely blind without any visual prodrome.
- **Diagnosis:** Temporal artery biopsy remains the standard to confirm the diagnosis. However, because inflammation in the temporal arteries can affect only some segments, biopsy results can be falsely negative.
- If a diagnosis of extracranial GCA is suspected, echocardiography, CT, or MRI are recommended. Studies with PET scan have suggested that subclinical aortic inflammation is often present in patients with GCA.
- **Treatment:** When GCA is suspected, treatment with glucocorticoids should be started immediately and biopsy performed as soon as possible. Delaying biopsy for 14 days or more may not affect the accuracy of biopsy study. Treatment should never be withheld while awaiting the results of biopsy study.

N.B: Polymyalgia rheumatica is another rheumatologic condition that occur independently or in conjunction with GCA. It is characterized by stiffness and pain in the proximal joints (hips and shoulders), typically worse in the morning and better with activity. Neurologic examination shows normal muscle power.

Takayasu arteritis (Pulseless disease):

- Takayasu arteritis is a rare, large-vessel vasculitis of unknown aetiology, characterized by granulomatous inflammation of the vessel wall, which is more commonly seen in Asian countries and typically affecting young women.
- The thoracic aorta and its major branches are the most frequent locations of the disease, followed by the abdominal aorta.
- **Clinical features:** (*spectrum of symptoms and signs, ranging from back- or abdominal pain with fever to acute severe aortic insufficiency, or to an incidentally identified large thoracic aortic aneurysm*).
 - Diminished or absent pulses with limb claudications (in 84-96%), vascular bruits (80-94%).
 - Hypertension (33-83%) usually reflecting renal artery stenosis.
 - Congestive heart failure associated with hypertension and aortic regurgitation.
 - Takayasu retinopathy (37%).
 - Pulmonary artery involvement (14-100%).
- **Complications:** The most important complications are: Takayasu retinopathy, secondary hypertension, aortic regurgitation, and aneurysm formation.
- **Role of imaging:**
 - Angiography remains the gold standard for confirming the diagnosis and planning the treatment.
 - In the case of suspicion of Takayasu arteritis, imaging the entire aorta is of critical importance, to establish the diagnosis.
 - In the early phase of Takayasu's arteritis, the thickening of vascular wall of the aorta or pulmonary artery can be detected by CT or MRI (due to arterial wall oedema). This finding could be misdiagnosed as an IMH). In the chronic stage, the aortic wall may become calcified, best assessed by CT.

- Color Doppler ultrasonography plays an important role for screening, detection and follow-up of carotid and subclavian arteries where it is easy to discriminate between atherosclerotic and inflammatory lesions
- **Laboratory findings:** Inflammation biomarkers (such as CRP and ESR) are elevated in approximately 70% of patients in acute phase and 50% in the chronic phase of the disease. Pentraxin-3 may have a better accuracy in differentiating the active- from the inactive phase of Takayasu arteritis.
- **Treatment:**
 - **Medical treatment** is to control active inflammation and minimize arterial injury. Prednisolone (1 mg/kg/day, max dose 60 mg/day) is the first line agent, with gradual tapering. Adjunctive steroid sparing immunosuppression (e.g methotrexate, azathioprine, and anti-TNF-alpha agents) is required in the majority of patients to minimize steroid-related complications and control disease progression, particularly as there is considerable risk of relapse when steroid treatment is stopped.
 - **Surgical treatment:** With symptomatic stenotic or occlusive lesions, it appears appropriate and often necessary to revascularize. The indications for considering intervention include uncontrolled hypertension as a consequence of renal artery stenosis, severe symptomatic coronary artery or cerebrovascular disease, severe aortic regurgitation or coarctation, stenotic or occlusive lesions resulting in critical limb ischemia, and aneurysms at risk of rupture.

Aortic tumors

- Primary malignant tumours of the aorta are an extremely rare class of sarcomas exhibiting a wide histopathological heterogeneity.
 - Intimal sarcomas, the most common, are derived from endothelial cells (angiosarcoma) or from myofibroblasts.
 - Leiosarcomas and fibrosarcomas originate from the media or adventitia of the aortic wall.
- **Diagnosis and workup:**
 - The most characteristic and frequently reported clinical presentation of an intimal angiosarcoma of the aorta is the embolic occlusion of the mesenteric or peripheral artery.

- After a cardiac source of the embolism is ruled out, contrast-enhanced MRI of the thoracic and abdominal aorta should be performed, as this investigation is the most sensitive diagnostic tool for detection of an aortic tumour.
- If an aortic lesion is found that is suggestive of a sarcoma, additional ultrasound examination may demonstrate inhomogeneity of the lesion, which is atypical for a mural thrombus.
- If the diagnosis of an aortic sarcoma is suspected, bone scintigraphy is recommended owing to the high prevalence of bone metastasis.
- **Prognosis:** The prognosis for aortic sarcomas is poor, with metastatic disease leading to death in a short time in most patients. Mean survival from the time of diagnosis is 16 ± 2.4 months.

Important trials in Aortic diseases:

Table 25-22: Clinical trials in aortic diseases:

| Trial (date) | Summary |
|--------------------------|--|
| EVAR (2010) | <p>Aim: <i>To compare the long-term results of endovascular versus open repair of large abdominal aneurysms.</i></p> <p>Study: <i>1252 patients with large abdominal aortic aneurysms (≥ 5.5 cm in diameter) were randomly assigned to undergo either endovascular or open repair. Endovascular repair of abdominal aortic aneurysm was associated with a significantly lower operative mortality than open surgical repair. However, no differences were seen in total mortality or aneurysm-related mortality in the long term. Endovascular repair was associated with increased rates of graft-related complications and reinterventions and was more costly.</i></p> |
| EVAR 2 (2010) | <p>Aim: <i>To evaluate treatment of abdominal aortic aneurysms by endovascular repair compared with conservative therapy among patients ineligible for open surgery.</i></p> <p>Study: <i>404 patients with large abdominal aortic aneurysms (≥ 5.5 cm in diameter) who were considered to be physically ineligible for open repair were randomly assigned to undergo either endovascular repair or no repair. Endovascular repair of abdominal aortic aneurysm was associated with a significantly lower rate of aneurysm-related mortality than no repair. However, endovascular repair was not associated with a reduction in the rate of death from any cause. The rates of graft-related complications and reinterventions were higher with endovascular repair, and more costly.</i></p> |
| DREAM (2010) | <p>Aim: <i>To evaluate treatment of abdominal aortic aneurysms by open repair compared with endovascular repair.</i></p> <p>Study: <i>351 patients with abdominal aortic aneurysms were randomly assigned to undergo open repair and to undergo endovascular repair. Six years after randomization, endovascular and open repair of abdominal aortic aneurysm resulted in similar rates of survival. The rate of secondary interventions was significantly higher for endovascular repair.</i></p> |

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Chapter 26:

Peripheral Arterial Disease

The term 'peripheral arterial diseases' (PAD) encompasses all arterial diseases other than coronary arteries and the aorta. This should be clearly distinguished from the term 'peripheral artery disease', which is often used for lower extremity artery disease (LEAD). Indeed, other peripheral localizations, including the carotid and vertebral, upper extremities, mesenteric and renal arteries, are also frequently affected, mainly by atherosclerosis, and complete the family of PADs.

Epidemiology and risk factors:

- The risk of different localizations of PADs increases sharply with age and with exposure to major CV risk factors, including smoking, hypertension, dyslipidaemia and diabetes.
- The strength of association between each risk factor and each vascular territory is variable, but all the major risk factors should be screened and considered.
- When a vascular territory is affected by atherosclerosis, not only is the corresponding organ endangered (e.g. the brain for carotid artery disease), but also the total risk of any CV event is increased (e.g. coronary events).

Diagnostic approach:

▪ Clinical history:

- **Personal history** should always be assessed for the evaluation of:

CV risk factors and comorbidities: Hypertension, Diabetes, Dyslipidemia, Smoking, Prior CVD, Chronic kidney disease, Sedentary life, Dietary habits, History of cancer radiation therapy.

Symptoms related to different vascular territories:

- Arm exertion pain, particularly if associated with dizziness or vertigo.
 - Symptoms suggesting angina, dyspnea.
 - Abdominal pain, particularly if related to eating and associated with weight loss.
 - Walking impairment/claudication: chronic; triggered by exercise, uphill rather than downhill, quickly relieved with rest.
 - Poorly healing wounds of the extremities.
 - Erectile dysfunction.
- **Family history** should be assessed for history of CAD or PAD and premature CVD (established diagnosis of CVD in first degree male relatives before 55 years or female relatives before 65 years).
 - **Clinical examination:** *Physical examination alone is of relatively poor sensitivity and reproducibility*
 - Upper extremities: Careful inspection (i.e colour, skin integrity), Palpation of UL pulses, Blood pressure measurement of both arms.
 - Lower extremities: Careful inspection (i.e colour, calf hair loss and muscle atrophy, presence of any cutaneous lesion), Palpation of LL pulses.
 - Peripheral neuropathy assessment in case of diabetes or LEAD: sensory loss (monofilament testing), ability to detect pain and light touch, vibration impairment; deep tendon reflexes examination; sweating.
 - **Laboratory testing:** Blood count, Fasting plasma glucose, glycated hemoglobin, lipid profile, Kidney function test, Uris acid, Urine analysis (to detect proteinuria), Lipoprotein (a) if there is a family history of premature cardiovascular disease.

Treatment approach:

Best medical therapy (BMT) includes CV risk factor management, best pharmacological therapy, and nonpharmacological measures (e.g smoking cessation, healthy diet, weight loss and regular physical exercise).

| Table 26-1: ESC Recommendations for medical therapy in patients with peripheral arterial disease: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| General principles: | | |

| | | |
|---|------------|----------|
| <i>Smoking cessation is recommended in all patients with PADs.</i> | I | B |
| <i>Healthy diet and physical activity are recommended for all patients with PADs.</i> | I | C |
| <i>Statins are recommended in all patients with PADs.</i> | I | A |
| <i>In patients with PADs, it is recommended to reduce LDL-C to < 70 mg/dL (1.8 mmol/L) or decrease it by ≥ 50% if baseline values are 70–135 mg/dL (1.8–3.5 mmol/L).</i> | I | C |
| <i>In diabetic patients with PADs, strict glycemic control (HbA1c ≤ 6.5%) is recommended.</i> | I | C |
| <i>Antiplatelet therapy is recommended in patients with symptomatic PADs.</i> | I | C |
| <i>In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg.</i> | I | A |
| <i>ACEIs or ARBs should be considered as first-line therapy ⁽¹⁾ in patients with PADs and hypertension.</i> | IIa | B |
| <i>β-Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant coronary artery disease and/or heart failure</i> | IIa | B |
| Carotid artery disease: | | |
| <i>In patients with symptomatic carotid stenosis, long-term SAPT is recommended.</i> | I | A |
| <i>DAPT (with aspirin and clopidogrel) is recommended for at least 1 month after CAS.</i> | I | B |
| <i>In patients with asymptomatic > 50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low.⁽²⁾</i> | IIa | C |
| Lower extremities artery disease: | | |
| <i>Long-term SAPT is recommended in: (1) symptomatic patient, (2) all patients who have undergone revascularization and (3) after infra-inguinal bypass surgery.</i> | I | C |

(1) Calcium channel blockers should be proposed in black individuals.

(2) With the exception of patients with an indication for long-term OAC.

| | | |
|---|------------|----------|
| <i>In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.</i> | IIb | B |
| <i>Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass.</i> | IIb | B |
| <i>DAPT (with aspirin and clopidogrel) for at least 1 month should be considered after infra-inguinal stent implantation.</i> | IIa | C |
| <i>DAPT (with aspirin and clopidogrel) may be considered in below-the-knee bypass with a prosthetic graft.</i> | IIb | B |
| <i>Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated ⁽¹⁾ asymptomatic LEAD.</i> | III | A |
| Antithrombotic therapy for PADs patients requiring oral anticoagulant: | | |
| <i>In patients with PADs and AF, OAC:</i> | | |
| ○ <i>Is recommended when the CHA2DS2-VASc score is ≥ 2</i> | I | A |
| ○ <i>Should be considered in all other patients.</i> | IIa | B |
| <i>In patients with PADs who have an indication for OAC (e.g. AF or mechanical prosthetic valve), oral anticoagulants alone should be considered.</i> | IIa | B |
| <i>After endovascular revascularization, aspirin or clopidogrel should be considered in addition to OAC for at least 1 month if the bleeding risk is low compared with the risk of stent/graft occlusion.</i> | IIa | C |
| <i>After endovascular revascularization, OAC alone should be considered if the bleeding risk is high compared with the risk of stent/graft occlusion.</i> | IIa | C |
| <i>OAC and SAPT may be considered beyond 1 month in high ischemic risk patients or when there is another firm indication for long-term SAPT.</i> | IIb | C |

(1) Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multisite artery diseases)

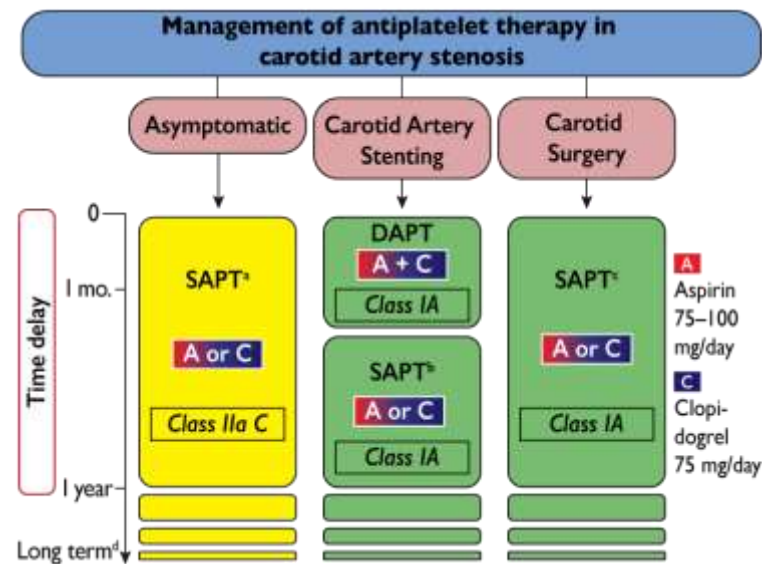


Figure 26-1: Management of antithrombotic treatment in patients with carotid artery stenosis. DAPT = dual antiplatelet therapy, a daily combination of aspirin (75–100mg) and clopidogrel (75mg); CAS = carotid artery stenting; SAPT = single antiplatelet therapy; TIA = transient ischaemic attack. **(A)** At the exception of patient at very high bleeding risk. **(B)** DAPT may be used if another indication supersedes that of carotid artery stenting such as ACS or PCI of less than 1 year. **(C)** In case of recent minor stroke or TIA, A loading dose of aspirin (300 mg) and/or clopidogrel (300/600 mg) is recommended at the acute phase of stroke/TIA or during CAS. **(D)** Stands for as long as it is well tolerated. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

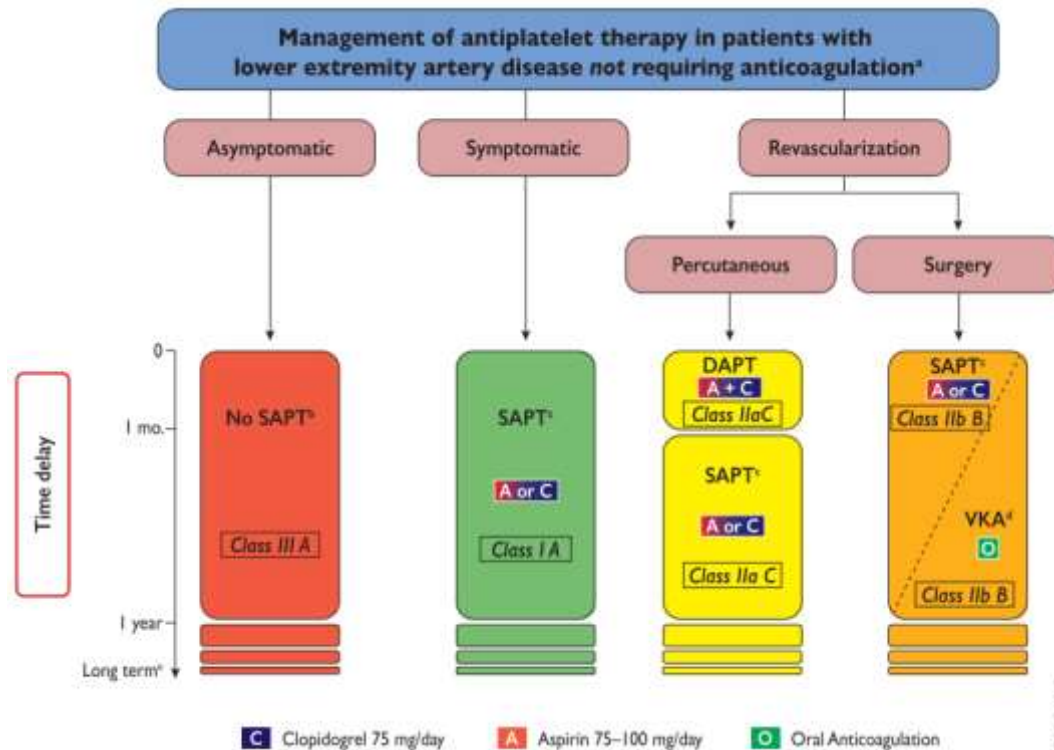


Figure 26-2: Antiplatelet therapy in patients with lower extremity artery disease. (A) e.g. concomitant AF or mechanical valve prosthesis. (B) SAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease). (C) DAPT may be considered in patients with recent ACS and/or PCI (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization. (D) Evidence is weak and bleeding doubles as compared to SAPT. (E) Stands for as long as it is well tolerated. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

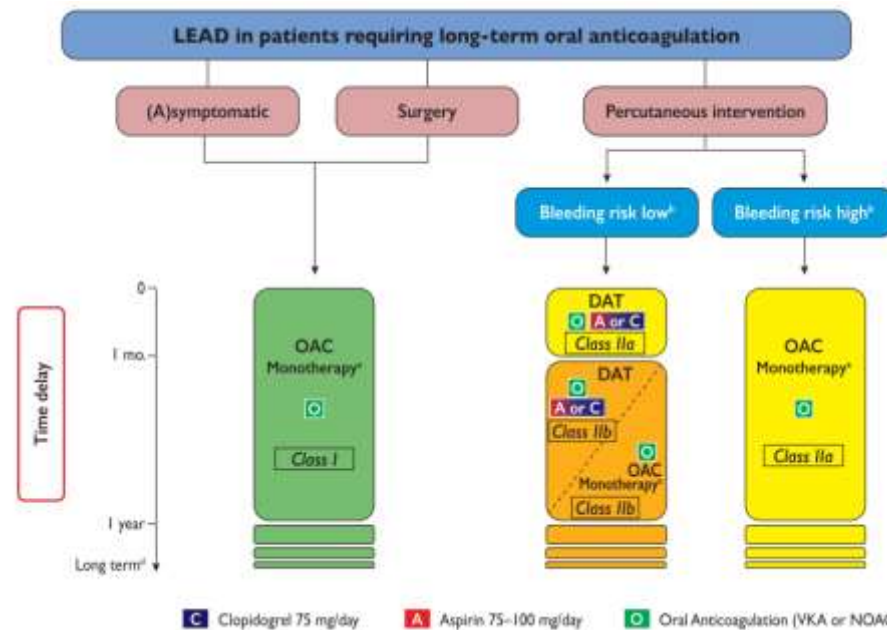


Figure 26-3: Antithrombotic therapy in patients with LEAD requiring oral anticoagulation. (A) DAT may be considered in high ischaemic risk patients defined as prior stent thrombosis, acute limb ischaemia on OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization). (B) Compared to the risk for stroke/CLTI due to stent/graft occlusion. (C) Stands for as long as it is well tolerated. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

Extracranial Carotid artery disease

- Carotid artery stenosis refers to a $\geq 50\%$ stenosis of the extracranial internal carotid artery (ICA), with stenosis severity estimated using the NASCET method. Of all strokes, 10–15% follow thromboembolism from a 50–99% internal carotid artery stenosis.

- Carotid stenosis is defined as ‘**symptomatic**’ if associated with stroke/TIA in the preceding 6 months and ‘**asymptomatic**’ if no prior stroke/TIA or occurred > 6 months ago.
- In patients with TIA/stroke, urgent imaging of the brain and supra-aortic vessels is mandatory. DUS is usually the first-line carotid imaging modality to assess extracranial ICA stenoses.
- In patients with TIA/stroke with 50-99% ICA stenosis, Echocardiography and 24-72 hrs rhythm monitoring remains suitable to detect the potential source of cardioembolism, but this should not delay any carotid intervention.
- **Features associated with increased risk of stroke in patients with asymptomatic carotid stenosis**⁽¹⁾: Contralateral TIA/stroke, Ipsilateral silent infarction, Ultrasound imaging features (Stenosis progression (> 20%), Spontaneous embolization on transcranial Doppler, Impaired cerebral vascular reserve, Large plaques⁽²⁾, Echolucent plaques, Increased hypoechogenic plaque area), MRA features (Intraplaque hemorrhage, Lipid-rich necrotic core).
- **Features associated with increased risk of stroke in patients with symptomatic carotid stenosis**: increasing age (especially > 75 years), symptoms within 14 days, male sex, hemispheric (vs. retinal) symptoms, cortical (vs. lacunar) stroke, increasing number of medical comorbidities, irregular stenoses, increasing stenosis severity, contralateral occlusion, tandem intracranial stenoses and a failure to recruit intracranial collaterals.

| Table 26-2: ESC Recommendations for management of extracranial carotid artery disease: | | |
|---|----------|----------|
| Recommendations | Class | Level |
| Imaging of extracranial carotid arteries: | | |
| <i>DUS (as first-line imaging), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.</i> | I | B |

(1) Age is not a predictor of poorer outcome (ACST trial).

(2) More than 40 mm² on digital analysis

| | | |
|--|-----|---|
| When Carotid Artery stenting (CAS) or Carotid Endarterectomy (CEA) is considered, it is recommended that any DUS study be followed by either MRA or CTA to confirm DUS stenosis estimation, evaluate the aortic arch as well as the extra- and intracranial circulation. | I | B |
| Asymptomatic carotid artery disease: | | |
| In 'average surgical risk' patients with an asymptomatic 60–99% stenosis, | | |
| ○ CEA should be considered. | IIa | B |
| ○ CAS may be considered as an alternative to CEA. | IIb | B |
| in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are < 3% and the patient's life expectancy is > 5 years. | | |
| In asymptomatic patients who have been deemed 'high risk for CEA' ⁽¹⁾ and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are < 3% and the patient's life expectancy is > 5 years. | IIa | B |
| Symptomatic carotid artery disease (Stroke or TIA occurring within 6 months): | | |
| Carotid Endarterectomy (CEA): | | |
| ○ is recommended in symptomatic patients with 70–99% carotid stenoses, | I | A |
| ○ should be considered in symptomatic patients with 50–69% carotid stenoses, provided the documented procedural death/stroke rate is < 6%. | IIa | A |

(1) **High surgical risk** was defined as Age > 80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral ICA occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

| | | |
|---|------------|----------|
| <i>CAS should be considered In symptomatic patients with a 50–99% stenosis who are considered ‘high risk for CEA’, provided the documented procedural death/stroke rate is < 6%.</i> | IIa | B |
| <i>When revascularization is indicated in ‘average surgical risk’ patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is < 6%.</i> | IIb | B |
| <i>When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.</i> | I | A |
| <i>Revascularization is not recommended in patients with a < 50% carotid stenosis.</i> | III | A |
| <i>The use of embolic protection devices (EPD) should be considered in patients undergoing carotid artery stenting.</i> | IIa | C |

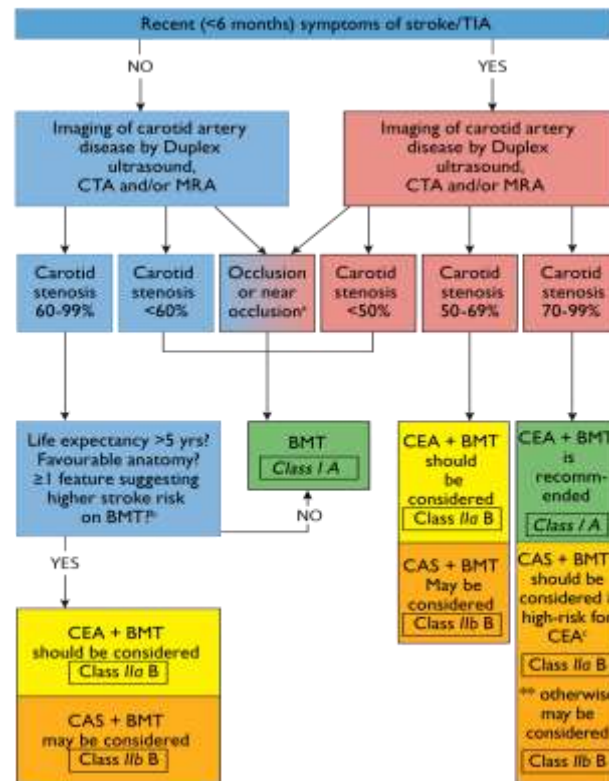


Figure 26-4: Management of extracranial carotid artery disease. BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack. **A)** With post-stenotic internal carotid artery narrowed to the point of near occlusion. **C)** Age > 80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

Extracranial Vertebral artery disease

Up to 20% of ischemic cerebrovascular events involving the posterior circulation are related to vertebral artery disease. CTA/MRA have a higher sensitivity and specificity (95%) than DUS (sensitivity 70%). Vertebral ostial stenoses are overestimated by MRA, while underestimated by CTA. Despite these limitations, DSA is rarely required for diagnostic purposes. DUS can be used to assess stenosis progression and to follow patients after revascularization therapies.

Table 26-3: ESC Recommendations for management of vertebral artery stenoses:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with symptomatic extracranial vertebral artery stenoses, revascularization may be considered for lesions $\geq 50\%$ in patients with recurrent ischemic events despite optimal medical management.</i> | IIb | B |
| <i>Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.</i> | III | C |

Upper extremity artery disease (UEAD)

Upper extremity artery disease due to atherosclerosis is mostly situated at the level of the brachiocephalic trunk, the subclavian and axillary arteries. However, UEAD can be caused by a number of conditions, involving different levels of the upper extremity arterial system.

- The most common manifestation for subclavian arterial occlusive disease is unequal arm pressures. A difference of ≥ 15 mmHg is highly suspicious for subclavian stenosis. It is not uncommon to detect this occlusive disease in asymptomatic patients.
- Subclavian steal syndrome due to flow reversal in the vertebral artery, which is worsened by exercising the arm, can evoke symptoms of vertebrobasilar insufficiency (dizziness, vertigo, blurred vision, alternating hemiparesis, dysphasia, dysarthria, confusion, and loss of consciousness, drop attacks, ataxia or other postural disturbances including sensory and visual changes).

Patients with coronary bypass with an internal mammary artery can develop symptoms of myocardial ischemia as the manifestation of subclavian steal syndrome.

- Brachiocephalic occlusive disease can also lead to stroke related to the carotid and vertebral territories. Ischemic arm symptoms are characterized by crampy pain on exercise- also referred to as arm claudication. In more severe cases -especially in more distal disease- rest pain and digital ischemia with gangrene can develop.

Diagnostic methods:

- Duplex ultrasonography: The proximal location of subclavian arterial occlusive disease makes DUS challenging. However, it is of particular value in differentiating occlusion from stenosis, in determining the direction of the vertebral blood flow, and in screening for concurrent carotid artery stenosis.
- Computed tomography angiography: CTA is an excellent imaging tool for supra-aortic lesions.
- Magnetic resonance angiography: MRA can be used to distinguish antegrade from retrograde perfusion. Assessment of antegrade and retrograde flow is particularly helpful when steal syndrome is suspected. MRA is also useful for follow-up studies.
- Digital subtraction angiography: DSA is a fluoroscopic technique used extensively in interventional radiology for visualizing blood vessels. Radiopaque structures such as bones are eliminated ("subtracted") digitally from the image, thus allowing for an accurate depiction of the blood vessels. DSA was considered the gold standard in imaging. Its main use is in combination with endovascular therapy.
- Positron emission tomography: PET is useful for the diagnosis of arteritis (Takayasu disease, giant cell arteritis) but not for assessment of atherosclerotic lesions in clinical practice.

Revascularization:

- **Indications:** Revascularization is indicated in symptomatic patients with TIA/stroke, coronary subclavian steal syndrome, ipsilateral haemodialysis access dysfunction or impaired quality of life. Revascularization should be considered in asymptomatic patients with planned CABG using the internal mammary artery, those with ipsilateral haemodialysis access, as well as asymptomatic patients with significant bilateral subclavian stenosis/occlusion for adequate BP surveillance.

- **Technique:** both endovascular and surgical procedures are available. An endovascular approach is often the default strategy. There are no RCTs comparing endovascular vs. open repair. The risk of severe complications, including vertebrobasilar stroke, is low with both approaches.

In endovascular strategy, stenting was superior to angioplasty alone, with a higher patency rate at 1 year indicated by the absence of events. Technical success of endovascular therapy is 100% when treating stenosis and 80–95% when treating occlusions.

Medical therapy:

- Risk factor control and BMT are recommended in all patients with symptomatic UEAD to reduce CV risk.
- In symptomatic patients with contraindications for endovascular therapy or open surgery, prostanoid infusion or thoracic sympathectomy may be considered.

Table 26-4: ESC Recommendations for management of subclavian artery stenosis:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In symptomatic patients with subclavian artery stenosis/occlusion, revascularization should be considered.</i> | IIa | C |
| <i>In symptomatic patients with a stenotic/ occluded subclavian artery, both revascularization options (stenting or surgery) should be considered and discussed case by case according to the lesion characteristics and patient's risk.</i> | IIa | C |
| <i>In asymptomatic subclavian artery stenosis, revascularization:</i> | | |

| | | |
|--|------------|----------|
| ○ <i>should be considered in the case of proximal stenosis in patients undergoing CABG using the ipsilateral internal mammary artery</i> | IIa | C |
| ○ <i>should be considered in the case of proximal stenosis in patients who already have the ipsilateral internal mammary artery grafted to coronary arteries with evidence of myocardial ischaemia</i> | IIa | C |
| ○ <i>should be considered in the case of subclavian artery stenosis and ipsilateral arterio- venous fistula for dialysis.</i> | IIa | C |
| ○ <i>may be considered in the case of bilateral stenosis in order to be able to monitor blood pressure accurately.</i> | IIb | C |

Mesenteric artery disease

Acute mesenteric ischemia:

Acute thromboembolic occlusion affects mostly the superior mesenteric artery. It is more often related to embolism than to thrombotic occlusion.

Diagnosis:

it is associated with the clinical triad of: **(1)** severe abdominal pain with minimal findings at examination, **(2)** bowel emptying (often both vomiting and diarrhea) and **(3)** the presence of a source of embolus (e.g. AF).

D-dimer is highly sensitive (96%), but it lacks specificity (40%). Lactate is metabolized by the liver, explaining why it does not serve as an early warning. Lactate is elevated only after bowel gangrene has developed.

High-resolution CTA is a major breakthrough for the timely diagnosis of acute mesenteric ischemia, with 94% sensitivity and 95% specificity. It should be performed in arterial and venous phases, with 1 mm slices. Elevated creatinine levels are common but should not contraindicate CTA in the case of clinical suspicion. There is no role for ultrasound or invasive angiography in diagnosing acute mesenteric ischemia.

Treatment:

Most patients with an acute occlusion of the superior mesenteric artery require immediate revascularization to survive. Approximately 20–30% can survive with bowel resection only, especially with distal embolism. In other cases, revascularization must be attempted. Whether revascularization or bowel inspection (with possible resection) should be performed first is controversial. Data suggest that revascularization should be attempted first, unless there is serious peritonitis and septic shock.

| Table 26-5: ESC Recommendations for Management of Acute mesenteric Ischemia: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>In patients with suspected acute mesenteric ischemia, urgent CTA is recommended.</i> | I | C |
| <i>In patients with suspicion of acute mesenteric ischemia, the measurement of D-dimer should be considered to rule out the diagnosis.</i> | IIa | B |
| Treatment: | | |
| <i>In patients with acute thrombotic occlusion of the superior mesenteric artery, endovascular therapy should be considered as first-line therapy for revascularization.</i> | IIa | B |
| <i>In patients with acute embolic occlusion of the superior mesenteric artery, both endovascular and open surgery therapy should be considered.</i> | IIa | B |

Chronic mesenteric artery disease:

Chronic mesenteric artery disease is related to atherosclerosis as well as non-atherosclerotic conditions. Atherosclerosis is the leading cause (95%). Nonatherosclerotic causes includes fibromuscular disease, Dunbar syndrome (compression of the coeliac trunk by the arcuate ligament), and vasculitis.

Typically, patients affected by mesenteric artery disease have diffuse atherosclerotic disease including CAD.

Diagnosis:

The classic symptoms are **abdominal angina**, a clinical syndrome characterized by **postprandial** abdominal pain, weight loss, diarrhea or constipation. DUS is often the imaging tool of first choice. When a decision to treat CMI is made, an anatomical mapping of the lesions is needed, mostly using CTA.

Treatment:

There is no indication for prophylactic revascularization in patients with asymptomatic disease. In symptomatic CMI, it is not recommended to delay revascularization in order to improve the nutritional status.

Delayed revascularization has been associated with clinical deterioration, bowel infarction and sepsis from catheter-related complications. In most centres, angioplasty and stenting have become the first option, reserving open surgery for patients with failed endovascular therapy. Although endovascular therapy has been increasingly used, open surgery is still indicated in the following situations: after failed endovascular therapy without possibility for repeat endovascular therapy; extensive occlusion, calcifications or young patients with non-atherosclerotic lesions due to vasculitis or mid-aortic syndrome.

| Table 26-6: ESC Recommendations for management of chronic mesenteric artery disease: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>DUS is indicated as the first line diagnostic test in patients suspected of chronic mesenteric artery disease.</i> | I | C |
| <i>In patients with suspected CMI, occlusive disease of a single mesenteric artery makes the diagnosis unlikely and a careful search for alternative causes should be considered.</i> | IIa | C |
| Treatment: | | |
| <i>In patients with symptomatic multivessel CMI, revascularization is recommended.</i> | I | C |
| <i>In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.</i> | III | C |

Renal artery disease (RAD)

- RAD is generally considered when renal artery stenosis (RAS) is $\geq 60\%$, although additional functional assessment by hemodynamic criteria is advisable. The prevalence of RAD increases with advancing age and is mostly related to atherosclerosis. Less frequent causes of RAD are fibromuscular dysplasia (FMD) and arteritis. Atherosclerotic RAD is the most common cause of 'renovascular hypertension'.

Diagnosis:

- **Clinical signs** include: resistant hypertension, unexplained renal failure and, uncommonly, flash pulmonary oedema. Renal hypoperfusion causes a BP increase secondary to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). With unilateral RAS, the contralateral kidney increases sodium excretion and there is no sodium retention or volume overload. In patients with severe bilateral RAS or unilateral RAS in a single functioning kidney, renal failure and flash pulmonary oedema can occur.
- **Clinical situations where the diagnosis of RAS should be considered:**
 - Onset of hypertension before the age of 30 years and after 55 years
 - Hypertension with hypokalemia, in particular when receiving thiazide diuretics
 - Hypertension and abdominal bruit
 - Accelerated hypertension (sudden and persistent worsening of previously controlled hypertension)
 - Resistant hypertension
 - Malignant hypertension.
 - New azotemia or worsening renal function after the administration of an ACEIs/ARBs.
 - Unexplained hypotrophic kidney
 - Unexplained renal failure.
- **Imaging modality:** In clinical situations with high suspicion, DUS is usually the first-line imaging modality, although it may overestimate the degree of stenosis, followed by MRA and/or CTA, for the establishment of a RAD diagnosis. DSA remains the

gold standard for the diagnosis of RAS. A systolic pressure gradient > 20 mmHg or a resting pressure ratio distal to the stenosis < 0.90 is considered to confirm significant stenosis in symptomatic patients.

- **Prognosis:** Life expectancy is reduced in patients with RAD without end-stage CKD, as they mostly die from an acute CV event. Patients who progress to end-stage CKD have even higher mortality rates.
- **Treatment:**
 - Renal revascularization does not generally improve blood pressure, renal or CV outcomes in patients with atherosclerotic RAD.
 - With few exceptions, medical therapy with antihypertensive agents, antiplatelet drugs and statins remains the cornerstone for management of patients with RAD.

| Table 26-7: ESC Recommendations for Management of renal artery stenosis: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Diagnosis: | | |
| <i>DUS (as first-line), CTA and MRA are recommended imaging modalities to establish a diagnosis of RAD.</i> | I | B |
| <i>DSA may be considered to confirm a diagnosis of RAD when clinical suspicion is high and the results of non-invasive examinations are inconclusive.</i> | IIb | C |
| <i>Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD.</i> | III | C |
| Treatment: | | |
| Medical therapy | | |
| <i>ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral RAS.</i> | I | B |
| <i>Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with renal artery disease.</i> | I | C |
| <i>ACEIs/ARBs may be considered in bilateral severe RAS and in the case of stenosis in a single functioning kidney, if well-tolerated and under close monitoring.</i> | IIb | B |

| Revascularization: | | |
|--|------------|----------|
| <i>Routine revascularization is not recommended in RAS secondary to atherosclerosis.</i> | III | A |
| <i>In cases of hypertension and/or signs of renal impairment related to renal arterial fibromuscular dysplasia, balloon angioplasty with bailout stenting should be considered.</i> | IIa | B |
| <i>Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema.</i> | IIb | C |
| <i>In the case of an indication for revascularization, surgical revascularization should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure or during open aortic surgery.</i> | IIa | B |

Lower extremity artery disease (LEAD)

▪ Clinical presentation:

- Most patients are asymptomatic (due to well-developed collaterals), detected either by a low ABI (< 0.90) or pulse abolition. Importantly, asymptomatic patients are still at high risk for cardiovascular events.
- Typical claudication is described as lower extremity discomfort, fatigue, or weakness initiated with exertion and resolving within 10 minutes of rest. It does not occur with prolonged standing per se; it does not occur at rest or at night unless there is also a severe exertional component and signs of CLI on exam. Isolated nocturnal leg cramps without exertional limitation are neuromuscular in origin.
- On physical exam, a normal posterior tibial pulse or dorsalis pedis pulse rules out significant PAD with 96% and 92% accuracy, respectively. A normal femoral pulse without bruit rules out aortoiliac PAD with over 90% accuracy.

Table 26-8: Clinical staging of LEAD:

| Fontaine Classification | | Rutherford classification | | |
|-------------------------|----------|---------------------------|----------|----------|
| Stage | Symptoms | Grade | Category | Symptoms |

| | | | | |
|------------|--|------------|----------|------------------------------|
| I | <i>Asymptomatic</i> | 0 | 0 | <i>Asymptomatic</i> |
| II | <i>IIa: Non-disabling Intermittent claudication</i> <i>IIb: disabling Intermittent claudication</i> | I | 1 | <i>Mild claudication</i> |
| | | | 2 | <i>Moderate claudication</i> |
| | | | 3 | <i>Severe Claudication</i> |
| III | <i>Ischemic rest pain</i> | II | 4 | <i>Ischemic rest pain</i> |
| IV | <i>Ulceration or gangrene</i> | III | 5 | <i>Minor tissue loss</i> |
| | | | 6 | <i>Major tissue loss</i> |

▪ **Diagnostic tests:**

• **Ankle-brachial index:**

○ **Who should have an ABI measurement in clinical practice?**

➤ Patients with clinical suspicion for LEAD:

- Lower extremities pulse abolition and/or bruit
- Typical intermittent claudication or symptoms suggestive for LEAD
- Non-healing lower extremity wound

➤ Patients at risk for LEAD because of the following clinical conditions:

- Atherosclerotic diseases: CAD, any PADs
- Other conditions: AAA, CKD, heart failure

➤ Asymptomatic individuals clinically-free but at-risk for LEAD:

- Men and women aged > 65 years
- Men and women aged < 65 years classified at high CV risk according to ESC guidelines
- Men and women aged > 50 years with family history for LEAD

○ **How to measure the ABI ?**

In supine position, with cuff placed just above the ankle, avoiding wounded zones. After a 5-10 minutes rest, the SBP is measured by a Doppler probe (5-10 MHz) on the posterior and anterior tibial (or dorsal pedis) arteries of each foot and on the brachial artery of each arm. Automated BP cuffs are mostly not valid for ankle pressure and may display overestimated results in case of low ankle pressure. The ABI of each leg is calculated by dividing the highest ankle SBP by the highest arm SBP.

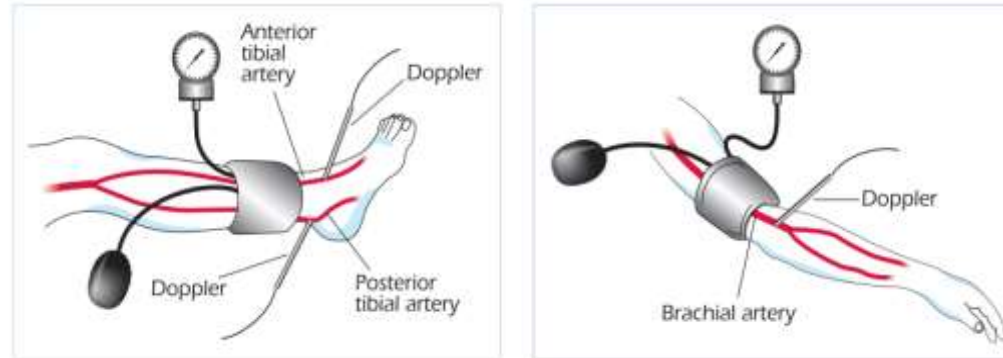


Figure 26-5: The Ankle-Brachial Index measurement. Source: 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

○How to interpret the ABI ?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg).
- For CV risk stratification, take the lowest ABI between the two legs.
- Interpretation:
 - Abnormal Low: $ABI < 0.9$
 - Borderline: $ABI = 0.9-1$
 - Normal: $ABI = 1-1.4$
 - Abnormal High: $ABI \geq 1.4$

○ **Notes:**

- An ABI < 0.90 has 75% sensitivity and 86% specificity to diagnose LEAD. Its sensitivity is poorer in patients with diabetes or end-stage CKD because of medial calcification.
- When clinically suspected, a normal ABI (> 0.90) does not definitely rule out the diagnosis of LEAD; further post-exercise ABI and/or DUS are necessary.
- In case of a high ABI (> 1.40) related to medial calcification, alternative tests such as toe pressure, toe- brachial index (TBI) or Doppler waveform analysis of ankle arteries are useful.
- **Treadmill test** (usually using the Strandness protocol) is an excellent tool for objective functional assessment and unmasking moderate stenosis, as well as for exercise rehabilitation follow-up. The test is stopped when the patient is unable to walk further because of pain, defining maximal walking distance. A post-exercise ankle SBP decrease > 30 mmHg or a post-exercise ABI decrease > 20% are diagnostic for LEAD.
- **Imaging:**
 - Ultrasound: DUS provides extensive information on arterial anatomy and haemodynamics. It must be combined with ABI measurement. It presents 85–90% sensitivity and > 95% specificity to detect stenosis > 50%. A normal DUS at rest should be completed by a post-exercise test when iliac stenosis is suspected, because of lower sensitivity.
 - Computed tomography angiography: the reported sensitivity and specificity of CTA to detect aorto-iliac and the femoro-popliteal stenoses > 50% are 96% and 98%, respectively.
 - Magnetic resonance angiography: The sensitivity and specificity of MRA are 95% for diagnosing segmental stenosis and occlusion. However, MRA tends to overestimate the degree of stenosis.

| Table 26-9: ESC Recommendations for diagnostics tests in patients of lower extremity artery disease: | | |
|--|--------------|--------------|
| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
| Ankle-brachial index: | | |

| | | |
|---|------------|----------|
| <i>Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.</i> | I | C |
| <i>In the case of incompressible ankle arteries or ABI > 1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording should be used.</i> | I | C |
| Treadmill testing (using the Strandness protocol) | | |
| <i>The treadmill test should be considered for the objective assessment of treatment to improve symptoms in claudicants.</i> | IIa | A |
| <i>In the case of typical or atypical symptoms suggestive of LEAD, the treadmill test should be considered for diagnostic confirmation and/or for baseline quantification of functional severity.</i> | IIa | B |
| Imaging: | | |
| <i>DUS is indicated as a first-line imaging method to confirm LEAD lesions.</i> | I | C |
| <i>DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.</i> | I | C |
| <i>Data from an anatomical imaging test should always be analysed in conjunction with symptoms and hemodynamic tests prior to a treatment decision.</i> | I | C |
| <i>DUS screening for AAA should be considered.</i> | IIa | C |

▪ **Treatment:**

○ **Medical therapy:**

- Smoking cessation provides the most noticeable improvement in walking distance when combined with regular exercise, especially when lesions are located below the femoral arteries.
- Statins significantly improve the CV prognosis and maximal walking distance in patients with intermittent claudications or CLTI.

- In subjects with hypertension, calcium antagonists or ACEIs/ARBs should be preferred because of their potential in peripheral arterial dilatation.
- Beta-blockers, in particular nebivolol, are safe in patients with intermittent claudications without negative effects on walking distance.
- **Revascularization Options:**

| Table 26-10: ESC Recommendations on revascularizations of LEAD: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Aortoiliac occlusive lesions: | | |
| <i>An endovascular-first strategy is recommended for short (i.e. < 5 cm) occlusive lesions.</i> | I | C |
| <i>In patients fit for surgery, aorto-(bi)femoral bypass should be considered in aorto-iliac occlusions.</i> | IIa | B |
| <i>An endovascular-first strategy should be considered in long and/or bilateral lesions in patients with severe comorbidities.</i> | IIa | B |
| <i>An endovascular-first strategy may be considered for aorto-iliac occlusive lesions if done by an experienced team and if it does not compromise subsequent surgical options.</i> | IIb | B |
| <i>Primary stent implantation rather than provisional stenting should be considered.</i> | IIa | B |
| <i>Open surgery should be considered in fit patients with an aortic occlusion extending up to the renal arteries.</i> | IIa | C |
| <i>In the case of ilio-femoral occlusive lesions, a hybrid procedure combining iliac stenting and femoral endarterectomy or bypass should be considered.</i> | IIa | C |
| <i>Extra-anatomical bypass may be indicated for patients with no other alternatives for revascularization.</i> | IIb | C |
| Femoropopliteal occlusive lesions: | | |

| | | |
|---|------------|----------|
| <i>An endovascular-first strategy is recommended in short (i.e. < 25 cm) lesions.</i> | I | C |
| <i>Primary stent implantation should be considered in short (i.e. < 25 cm) lesions.</i> | IIa | A |
| <i>Drug-eluting balloons may be considered in short (i.e. < 25 cm) lesions.</i> | IIb | A |
| <i>Drug-eluting stents may be considered for short (i.e. < 25 cm) lesions.</i> | IIb | B |
| <i>Drug-eluting balloons may be considered for the treatment of in-stent restenosis.</i> | IIb | B |
| <i>In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. ≥ 25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is > 2 years.</i> | I | B |
| <i>The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass.</i> | I | A |
| <i>When above-the-knee bypass is indicated, the use of a prosthetic conduit should be considered in the absence of any autologous saphenous vein.</i> | IIa | A |
| <i>In patients unfit for surgery, endovascular therapy may be considered in long (i.e. ≥ 25 cm) femoro-popliteal lesions</i> | IIb | C |
| Infrapopliteal occlusive lesions: | | |
| <i>In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage.</i> | I | C |
| <i>For revascularization of infra-popliteal arteries:</i> | | |
| - Bypass using the great saphenous vein is indicated | I | A |
| - endovascular therapy should be considered. | IIa | B |

▪ **Management of intermittent claudication (IC):**

- Claudication usually remains stable or improves with conservative management. At 5 years, only 20% of patients have progressive claudication, and only 4% progress to critical limb ischemia (CLTI). This explains why, in the absence of critical limb ischemia, revascularization is only justified for very severe claudication.

- Exercise therapy (ExT) is effective and improves symptoms and QOL and increases maximal walking distance. Supervised exercise therapy is more effective than unsupervised exercise therapy.
- Some antihypertensive drugs (e.g. verapamil), statins, antiplatelet agents and prostanoids (prostaglandins I2 and E1) have some favourable effects on walking distance and leg functioning.
- The anatomical location and extension of arterial lesions has an impact on revascularization options. Endovascular therapy should be restricted to patients who do not respond favourably to exercise therapy (e.g. after a 3-month period of ExT) or when disabling symptoms substantially alter daily life activities.

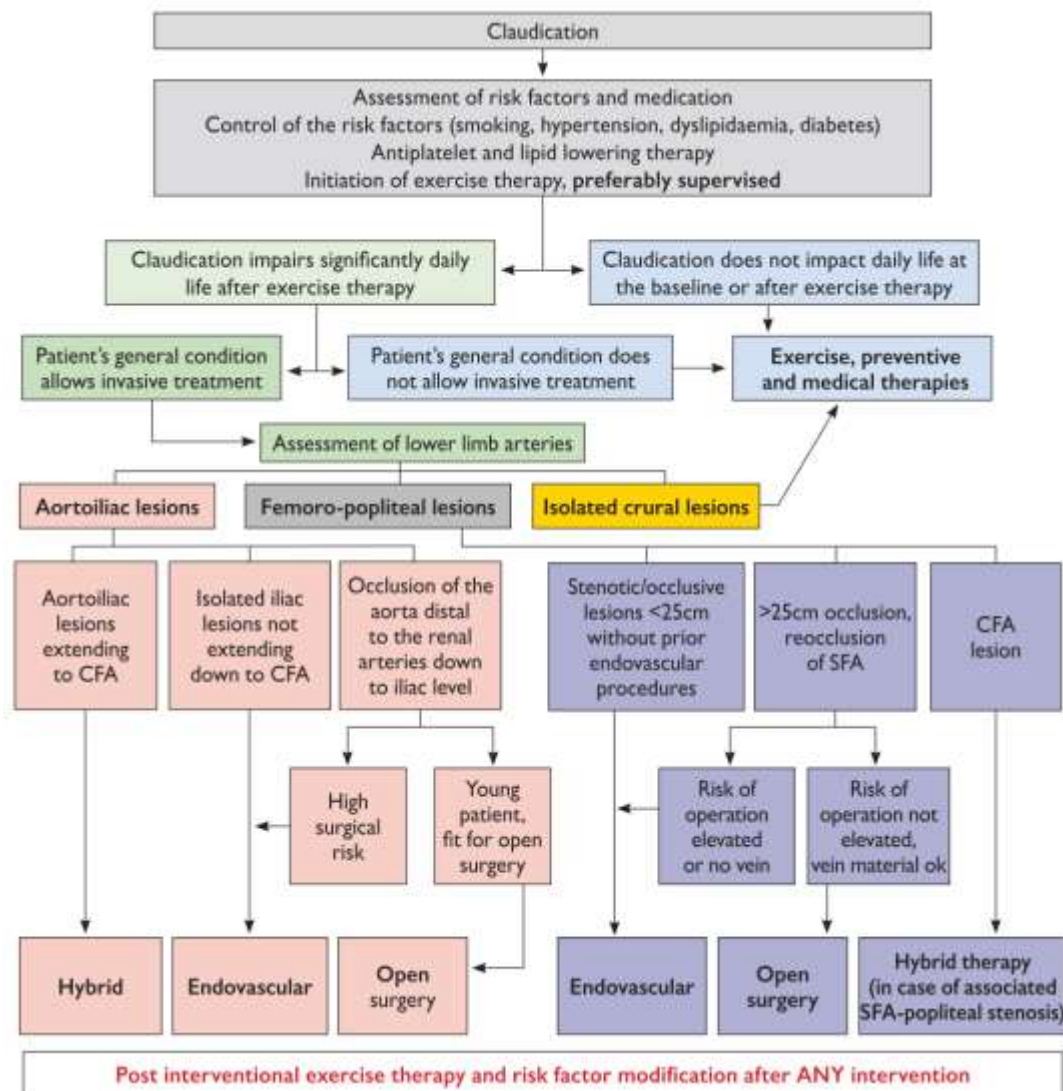


Figure 26-6: Management of patients with intermittent claudication related to atherosclerotic lower extremity artery disease (LEAD). CFA = common femoral artery; SFA = superficial femoral artery. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

| Table 26-11: ESC Recommendations for patients with intermittent claudication: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>On top of general prevention, statins are indicated to improve walking distance.</i> | I | A |
| <i>In patients with intermittent claudication:</i> | | |
| - supervised exercise training is recommended. | I | A |
| - unsupervised exercise training is recommended when supervised exercise training is not feasible or available. | I | C |
| <i>When daily life activities are compromised despite exercise therapy, revascularization should be considered.</i> | IIa | C |
| <i>When daily life activities are severely compromised, revascularization should be considered in association with exercise therapy.</i> | IIa | B |

▪ **Chronic limb-threatening ischemia (CLTI):**

CLTI is defined by the presence of ischemic rest pain, with or without tissue loss (ulcers, gangrene) or infection. When present, arterial ulcers are usually painful and are often complicated by local infection and inflammation. When pain is absent, peripheral neuropathy should be considered. While CLTI is a clinical diagnosis, it is often associated with an ankle pressure < 50 mmHg or toe pressure < 30 mmHg. CLTI is a marker for generalized, severe atherosclerosis, with a 3-fold increased risk of MI, stroke and vascular death as compared to patients with intermittent claudication.

○ **CLTI severity and started risk stratification: the WIfI classification**

The target population for this system includes any patient with:

- ischemic rest pain, typically in the forefoot with objectively confirmed hemodynamic studies (ABI < 0.40, ankle pressure < 50 mmHg, toe pressure < 30 mmHg, TcPO₂ < 30 mmHg),
- diabetic foot ulcer,
- non-healing lower limb or foot ulceration ≥ 2 weeks duration or

- gangrene involving any portion of the foot or lower limb.

The three primary factors that constitute and contribute to the risk of limb threat are wound (W), ischemia (I) and foot infection (fi).

| Table 26-12: Assessment of the risk of amputation: the WIFI classification | | | | |
|--|-------|--|-----------------------|---|
| Component | Score | Description | | |
| W (wound) | 0 | No ulcer (ischemic rest pain) | | |
| | 1 | Small, shallow ulcer on distal leg or foot without gangrene | | |
| | 2 | Deeper ulcer with exposed bone, joint or tendon ± Gangrenous changes limited to toes | | |
| | 3 | Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene | | |
| I (Ischemia) | | ABI | Ankle Pressure | Toe Pressure or TcPO₂ |
| | 0 | ≥ 0.80 | > 100 | ≥ 60 |
| | 1 | 0.60-0.79 | 70-100 | 40-59 |
| | 2 | 0.40-0.59 | 50-70 | 30-39 |
| | 3 | < 0.40 | < 50 | < 30 |
| FI (foot infection) | 0 | No symptoms/signs of infection | | |
| | 1 | Local infection involving only skin and subcutaneous tissue | | |
| | 2 | Local infection involving Deeper than skin and subcutaneous tissue | | |
| | 3 | Systemic inflammatory response syndrome | | |

N.B: ABI commonly underestimates the severity of PAD in CLI patients with predominantly infrapopliteal disease. This is related to the fact that tibial arteries are partially non-compressible (creating a falsely normal or elevated tibial pressure), but also to the fact that a substantial proportion of CLI patients have significant pedal/below-ankle disease, sometimes with a “desert” foot (narrow or occluded plantar and metatarsal arteries). Toe-brachial index (TBI) is more reliable than ABI in CLI patients and should be systematically measured in this context.

Table 26-13: ESC Recommendations for the management of Chronic limb-threatening ischemia:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.</i> | I | C |
| <i>In patients with CLTI, assessment of the risk of amputation is indicated.</i> | I | C |
| <i>In patients with CLTI and diabetes, optimal glycemic control is recommended.</i> | I | C |
| <i>For limb salvage, revascularization is indicated whenever feasible.</i> | I | B |
| <i>In CLTI patients with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularization.</i> | IIa | C |
| <i>In patients with CLTI, stem cell/gene therapy is not indicated.</i> | III | B |

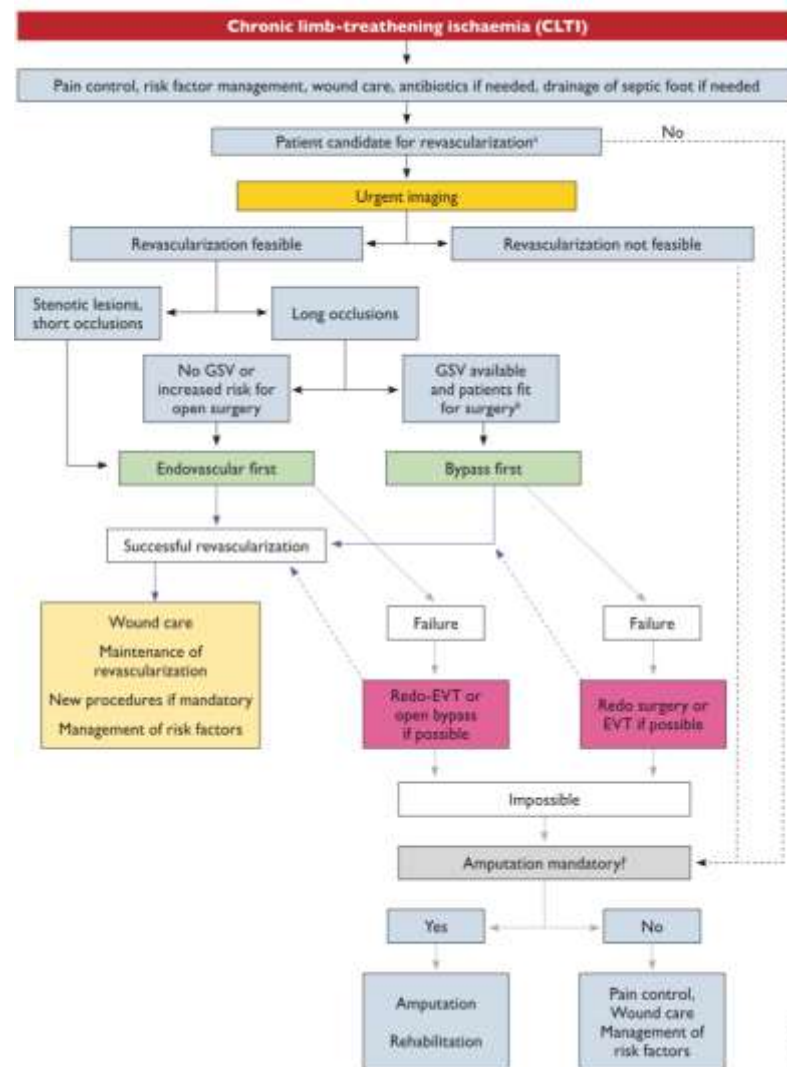


Figure 26-7: Management of patients with chronic limb-threatening ischaemia. EVT= endovascular therapy; GSV = great saphenous vein. **(A)** In bedridden, demented and/or frail patients, primary amputation should be considered. **(B)** In the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

▪ **Acute limb ischaemia (ALI):**

- ALI is rest ischemia that develops over hours, sometimes days (generally < 14 days), and is usually due to: **(i)** acute embolization from a cardiac or aortic origin (30% of cases), **(ii)** acute thrombosis of an underlying atherosclerotic stenosis or popliteal aneurysm (60% of cases), **(iii)** thrombosis in situ from a hypercoagulable state or traumatic injury/dissection, or **(iv)** graft thrombosis. Regardless of the underlying process, multiple distal emboli are characteristic of ALI.
- Once the clinical diagnosis is established, treatment with unfractionated heparin should be given, along with appropriate analgesia. The emergency level and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficits.

In the case of neurological deficit, urgent revascularization is mandatory; imaging should not delay intervention. DUS and DSA are mostly used in these situations.

- Different revascularization modalities can be applied, including percutaneous catheter-directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy) and surgical thrombectomy, bypass and/or arterial repair.

Owing to reduced morbidity and mortality, endovascular therapy is often preferred, especially in patients with severe comorbidities. Thrombus extraction, thrombo-aspiration and surgical thrombectomy are indicated in the case of neurological deficit, while catheter-directed thrombolytic therapy is more appropriate in less severe cases without neurological deficit.

Table 26-14: Clinical categories of acute limb ischemia:

| Grade | Category | Sensory loss | Motor deficit | Prognosis |
|------------|------------------------|-----------------------|-----------------------------|----------------------------------|
| I | Viable | None | None | No immediate threat |
| IIA | Marginally threatened | None or minimal | None | Salvageable if promptly treated |
| IIB | Immediately threatened | More than toes | Mild/ moderate | |
| III | Irreversible | Profound, anaesthetic | Profound, paralysis (rigor) | Major tissue loss Amputation. |

| | | | | |
|--|--|--|--|-----------------------------------|
| | | | | Permanent nerve damage inevitable |
|--|--|--|--|-----------------------------------|

Table 26-15: ESC Recommendations for management of acute limb ischemia:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In the case of neurological deficit, urgent revascularization is indicated.</i> | I | C |
| <i>In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision.</i> | I | C |
| <i>Heparin and analgesics are indicated as soon as possible.</i> | I | C |

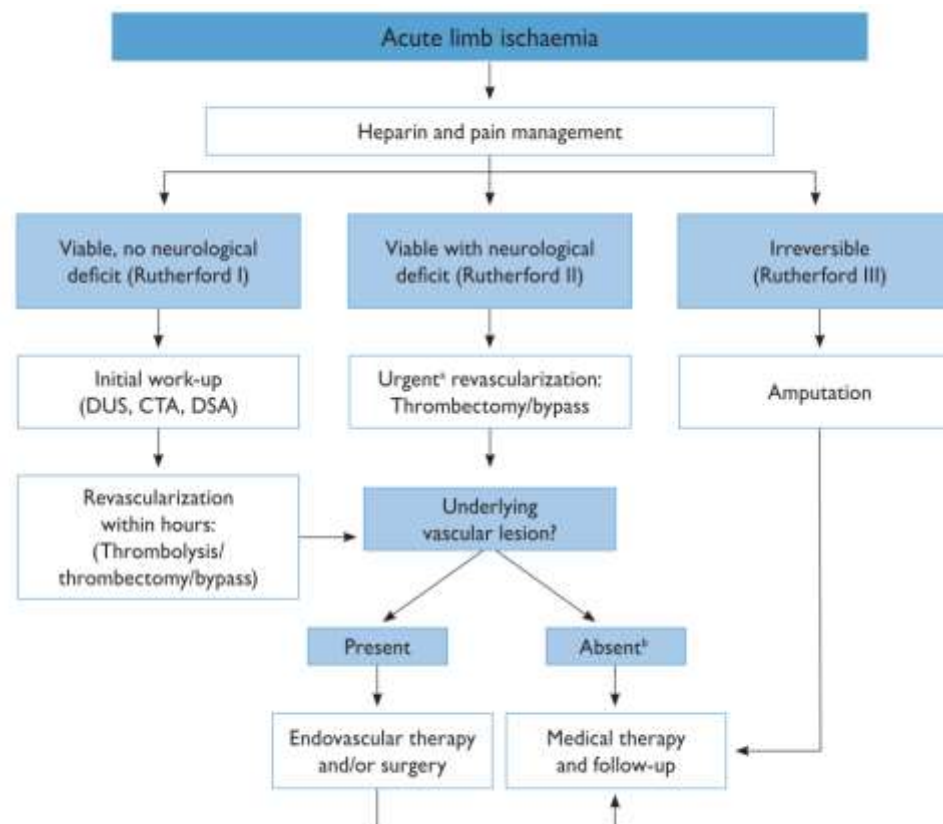


Figure 26-8: Management of acute limb ischaemia. CTA = computed tomography angiography; DSA = digital subtraction ultrasound; DUS = duplex ultrasound. **A)** Imaging should not delay revascularization. **B)** Specific etiological work-up is necessary (cardiac, aorta). **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

Multisite artery disease

▪ **Definition:**

Multisite artery disease (MSAD) is defined as the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories. It is common in patients with atherosclerotic involvement in one vascular bed, ranging from 10 to 15% in patients with CAD to 60 to 70% in patients with severe carotid stenosis or LEAD.

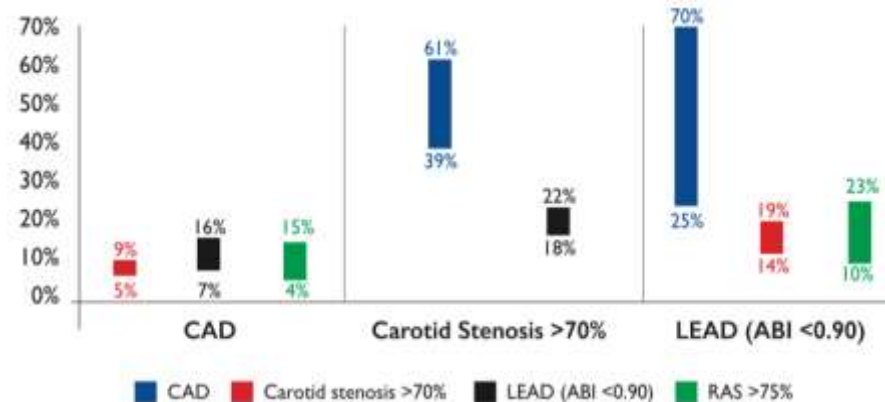


Figure 26-9: Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease. The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g. in patients with CAD, 5 - 9% of cases have concomitant carotid stenosis >70%). ABI = ankle-brachial index; CAD = coronary artery disease; LEAD = lower extremity artery disease; RAS = renal artery stenosis. **Source:** 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases.

▪ **Screening and management:**

MSAD is invariably associated with worse clinical outcomes; however, systematic screening for asymptomatic disease in additional vascular sites has not been proven to improve prognosis and is yet not indicated. In patients with any presentation of PADs, clinical assessment of symptoms and physical signs of other localizations and/or CAD is necessary and in case of clinical suspicion, further tests may be planned.

Screening for asymptomatic lesions may be interesting in some cases. This is the case for patients undergoing CABG, where ABI measurement may be considered especially when saphenous vein harvesting is planned, and carotid screening should be considered in a subset of patients at high risk of carotid artery disease.

Table 26-16: Indication for screening of associated atherosclerotic disease in additional vascular territories:

| | CAD | LEAD | Carotid |
|--------------------------|------------|------------|-----------------|
| CAD: | | | |
| Scheduled for CABG | | IIa | I or IIb |
| Not Scheduled for CABG | | IIb | NR |
| LEAD: | | | |
| Scheduled for CABG | I | | NR |
| Not Scheduled for CABG | NR | | NR |
| Carotid Stenosis: | | | |
| Scheduled for CABG | IIb | NR | |
| Not Scheduled for CABG | NR | NR | |

Table 26-17: ESC Recommendations for the management of carotid stenosis in patients undergoing CABG:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Screening for carotid artery stenosis Before CABG: | | |
| <i>In patients undergoing CABG, DUS is recommended in patients with a recent (< 6 months) history of TIA/stroke.</i> | I | B |

| | | |
|--|------------|----------|
| <i>In patients with no recent (< 6 months) history of TIA/stroke, DUS may be considered in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD or carotid bruit.</i> | IIb | B |
| <i>Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.</i> | III | C |
| Management of carotid stenosis Before CABG: | | |
| <i>It is recommended that the indication (and, if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.</i> | I | C |
| <i>In patients with a recent (< 6 months) history of TIA/stroke who are scheduled for CABG:</i> | | |
| ○ <i>Carotid revascularization (with CEA as the first choice) should be considered in patients with 50–99% carotid stenosis.</i> | IIa | B |
| ○ <i>Carotid revascularization is not recommended in patients with carotid stenosis <50%.</i> | III | C |
| <i>In neurologically asymptomatic patients scheduled for CABG:</i> | | |
| ○ <i>Routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.</i> | III | B |
| ○ <i>Carotid revascularization may be considered in patients with bilateral 70–99% carotid stenoses or 70–99% carotid stenosis + contralateral occlusion.</i> | IIb | B |
| ○ <i>Carotid revascularization may be considered in patients with a 70–99% carotid stenosis in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke in order to reduce stroke risk beyond the perioperative period.</i> | IIb | C |

▪ **Management of patients with LEAD and concomitant CAD:**

Table 26-18: ESC Recommendations for management of patients with LEAD and concomitant CAD

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention.</i> | I | C |
| <i>In patients with LEAD undergoing CABG, sparing the autologous great saphenous vein for potential future use for surgical peripheral revascularization should be considered.</i> | IIa | C |
| <i>In patients undergoing CABG and requiring saphenous vein harvesting, screening for LEAD should be considered.</i> | IIa | C |
| <i>In patients with CAD, screening for LEAD by ABI measurement may be considered for risk stratification.</i> | IIb | B |

Important trials in Peripheral vascular diseases:

| Table 26-19: Clinical trials in Peripheral vascular diseases: | |
|---|---|
| Trial (date) | Summary |
| Antithrombotic therapy: | |
| EUCLID (2017) | <p>Aim: To evaluate treatment with ticagrelor compared with clopidogrel among patients with PAD.</p> <p>Study: 13,865 patients with symptomatic peripheral artery disease were randomly assigned to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patients were eligible if they had an ABI ≤ 0.80 or had undergone previous revascularization of the lower limbs. No significant differences were found between ticagrelor and clopidogrel for reduction of cardiovascular or acute limb events.</p> |
| VOYAGER PAD (2020) | <p>Aim: To evaluate rivaroxaban/aspirin compared with placebo/aspirin among patients with lower extremity PAD undergoing revascularization.</p> <p>Study: 6564 patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. Rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone.</p> |
| Carotid artery stenosis: | |
| ACAS (2004) | <p>Aim: To assess the efficacy carotid endarterectomy for 5-year ipsilateral stroke in asymptomatic patients.</p> <p>Study: 3120 patients with mainly asymptomatic carotid stenosis $> 60\%$ randomized to immediate endarterectomy plus medical treatment versus medical treatment alone or until the operation became necessary. The incidence of</p> |

| | |
|----------------------|--|
| | <i>cerebral infarction can be reduced by endarterectomy, and forms the foundation for current clinical guidelines for asymptomatic patients.</i> |
| NASCET (1998) | <p>Aim: <i>To assess the benefit of carotid endarterectomy in patients with symptomatic moderate stenosis (stenosis of < 70%).</i></p> <p>Study: <i>2226 patients who had moderate carotid stenosis and transient ischemic attacks or nondisabling strokes on the same side as the stenosis (ipsilateral) within 180 days before study entry were stratified according to the degree of stenosis (50-69% or < 50%) and randomly assigned to undergo carotid endarterectomy or to receive medical care alone. Endarterectomy in patients with symptomatic moderate carotid stenosis of 50-69% yielded only a moderate reduction in the risk of stroke. Patients with stenosis < 50% did not benefit from surgery. Patients with severe stenosis (≥ 70%) had a durable benefit from endarterectomy at eight years of follow-up.</i></p> |
| CREST (2010) | <p>Aim: <i>To compare the outcomes of carotid-artery stenting with those of carotid endarterectomy among patients with symptomatic or asymptomatic carotid stenosis.</i></p> <p>Study: <i>2502 patients with symptomatic or asymptomatic carotid stenosis were randomly assigned to undergo carotid-artery stenting or carotid endarterectomy. The risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy.</i></p> |
| ACT-1 (2016) | <p>Aim: <i>To compare the outcomes of carotid endarterectomy versus stenting with embolic protection in patients with asymptomatic severe carotid-artery stenosis who were at standard risk for surgical complications.</i></p> <p>Study: <i>1453 asymptomatic patients aged ≤ 79 years who had severe carotid stenosis and were not considered to be at high risk for surgical complications were randomized to carotid-artery stenting with embolic protection and carotid endarterectomy. The primary composite endpoint of death, stroke, or MI within 30 days after the procedure or ipsilateral stroke within 1 year. Stenting was noninferior to endarterectomy with regard to the rate of the primary</i></p> |

| | |
|----------------------------|--|
| | <i>composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant differences between the study groups in the rates of non–procedure-related stroke, all stroke, and survival.</i> |
| ACST-1 (2010) | <p>Aim: <i>To assess the long-term effects of successful carotid endarterectomy (CEA) in asymptomatic patients.</i></p> <p>Study: <i>3120 asymptomatic patients aged < 75 years were randomly assigned to immediate CEA or deferral of a carotid procedure until a more definitive indication arose. Successful carotid endarterectomy in asymptomatic patients aged < 75 years reduces 10-year risk of stroke. Half of the risk reduction is in the reduction of disabling or fatal strokes.</i></p> |
| SPACE (2006) | <p>Aim: <i>To compare the carotid endarterectomy and carotid-artery stenting in patients with severe symptomatic carotid stenosis.</i></p> <p>Study: <i>1200 patients with symptomatic carotid-artery stenosis were randomly assigned within 180 days of TIA or moderate stroke (modified Rankin scale score of ≤ 3) to carotid-artery stenting or carotid endarterectomy. The primary endpoint was ipsilateral ischaemic stroke or death from time of randomisation to 30 days after the procedure. The trial failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy for the periprocedural complication rate.</i></p> |
| EVA-3S (2006) | <p>Aim: <i>To compare stenting with endarterectomy in patients with symptomatic carotid stenosis of at least 60%.</i></p> <p>Study: <i>The trial was stopped prematurely after the inclusion of 527 patients for reasons of both safety and futility. The rates of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting.</i></p> |
| ICSS (2015) | <p>Aim: <i>To compare stenting with endarterectomy in patients with symptomatic stenosis.</i></p> <p>Study: <i>1713 patients with symptomatic carotid stenosis were randomly assigned to open treatment with stenting or endarterectomy. The primary endpoint was fatal or disabling stroke in any territory. Long-term functional outcome and risk of fatal or disabling stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis.</i></p> |
| SAPPHIRE (2008) | <p>Aim: <i>To compare the safety and effectiveness of carotid artery stenting with an emboli-protection device to CEA in the treatment of carotid artery disease in patients at increased risk for surgery.</i></p> |

| | |
|--|---|
| | <p>Study: 334 patients who had either symptomatic $\geq 50\%$ carotid artery stenosis or asymptomatic $\geq 80\%$ stenosis were assigned to carotid artery stenting with the use of an emboli-protection device or endarterectomy. No significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli-protection device and those who underwent endarterectomy.</p> |
| ECST (1998) | <p>Aim: To assess the efficacy of carotid endarterectomy for ischemic stroke in symptomatic patients.</p> <p>Study: 2267 patients who had moderate carotid stenosis and TIA or nondisabling strokes on the same side as the stenosis within 180 days before study entry were randomly assigned either to undergo carotid endarterectomy or to receive medical care alone. Endarterectomy yielded only a moderate reduction in the risk of stroke. Patients with stenosis of less than 50% did not benefit from surgery. Patients with severe stenosis ($\geq 70\%$) had a durable benefit from endarterectomy at 8-years of follow-up.</p> |
| Other Peripheral arterial diseases: | |
| CORAL (2014) | <p>Aim: To determine the effects of renal-artery stenting on the incidence of important CV and renal adverse events.</p> <p>Study: 947 participants who had atherosclerotic renal-artery stenosis and either systolic hypertension while taking ≥ 2 antihypertensive drugs or CKD were randomly assigned to medical therapy plus renal-artery stenting or medical therapy alone. Renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy.</p> |
| ASTRAL (2009) | <p>Aim: To determine whether revascularization together with medical therapy improves renal function and other outcomes, as compared with medical therapy alone, in patients with atherosclerotic renal-artery stenosis.</p> <p>Study: 806 patients with atherosclerotic renovascular disease were randomly assigned either to undergo revascularization in addition to receiving medical therapy or to receive medical therapy alone. The primary outcome was renal function, as measured by the reciprocal of the serum creatinine level (a measure that has a linear relationship with creatinine clearance). No evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease.</p> |

| | |
|----------------------------|---|
| CLEVER (2011) | <p>Aim: To report the longer-term (18-month) efficacy of supervised exercise compared with stenting and optimal medical care in patients with claudication due to aortoiliac disease.</p> <p>Study: 111 patients with aortoiliac PAD randomly assigned to receive optimal medical care, medical care plus supervised exercise, or medical care plus stent revascularization. Both supervised exercise and stent revascularization had better 18-month outcomes than medical care. Supervised exercise and stent revascularization provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary PAD claudication treatment.</p> |
| BASIL (2005) | <p>Aim: To compare the outcome of bypass surgery and balloon angioplasty in patients with severe limb ischemia due to infra-inguinal disease.</p> <p>Study: 452 patients with severe limb ischemia due to infra-inguinal disease were randomly assigned to receive a surgery-first or an angioplasty-first strategy. The primary endpoint was amputation free survival. Bypass-surgery-first and a balloon-angioplasty-first strategy are associated with similar outcomes in terms of amputation-free survival, and in the short-term, surgery is more expensive than angioplasty.</p> |
| BASIL-2 (2023) | <p>Aim: To evaluate vein bypass compared with endovascular treatment in chronic limb-threatening ischemia due to infra-popliteal disease.</p> <p>Study: 345 patients with chronic limb-threatening ischemia were randomly assigned to receive either vein bypass (vein bypass group) or best endovascular treatment (best endovascular treatment group) as their first revascularization procedure. The best endovascular treatment first revascularization strategy was associated with a better amputation-free survival, which was largely driven by fewer deaths in the best endovascular treatment group. These data suggest that more patients with chronic limb-threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularization procedure to restore limb perfusion should be considered for a best endovascular treatment first revascularization strategy.</p> |
| BEST-CLI (2022) | <p>Aim: To assess the safety and effectiveness of surgery compared with endovascular intervention in chronic limb-threatening ischemia.</p> |

Study: 1,830 patients with chronic limb-threatening ischemia were randomized to either surgery with venous bypass or endovascular treatment, or surgery with an alternate bypass conduit or endovascular treatment. Surgical revascularization with a great saphenous venous conduit was superior to endovascular intervention in reducing major adverse limb events (including above-ankle amputations) or death, primarily driven by a reduction in major adverse limb events. When a great saphenous vein conduit was not available, outcomes were similar between surgery and endovascular therapies.

References and suggested readings:

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Section

IX

Preventive Cardiology

TO THE POINT

Cardiovascular Diseases Prevention

CVD prevention in clinical practice concentrate principally on risk and prevention of ASCVD. This includes risk factors, risk prediction, risk modifiers, as well as clinical conditions that often increase the likelihood of ASCVD.

Initially, CVD risk assessment or screening can be done opportunistically or systematically:

- **Opportunistic screening:** screening without a predefined strategy which is done for a person presents for some other reason. Opportunistic screening for ASCVD risk factors, such as BP or lipids, is effective at increasing detection rates and is recommended, although a beneficial effect on clinical outcome is uncertain.
- **Systematic screening:** formal screening programme, with call and recall of patients, which is done for general population or in targeted subpopulations such as subjects with type 2 DM, or family history of premature CVD. Systematic screening results in improvements in risk factors, but has no effect on CVD outcomes.

Risk factors:

- **Cholesterol:** The key attributes of LDL-C as a risk factor for ASCVD are:
 - Prolonged lower LDL-C is associated with lower risk of ASCVD, and the results of RCTs indicate that lowering LDL-C safely reduces CVD risk even at low LDL-C levels [e.g. LDL-C < 55 mg/dL].
 - The relative reduction in CVD risk is proportional to the absolute size of the change in LDL-C, irrespective of the drug(s) used to achieve such change.
 - The absolute benefit of lowering LDL-C depends on the absolute risk of ASCVD and the absolute reduction in LDL-C.
 - Non-HDL-C encompasses all atherogenic (apo-B-containing) lipoproteins. The relationship between non-HDL-C and CV risk is at least as strong as the relationship with LDL-C. Non-HDL-C levels contain, in essence, the same information as a measurement

of apo-B plasma concentration. Non-HDL-C is used as an input in the Systemic Coronary Risk Estimation 2 (SCORE2) and SCORE2-Older Persons (SCORE2-OP) risk algorithms.

- **Blood pressure:** Elevated BP is a risk factor for the development of CAD, HF, cerebrovascular disease, LEAD, CKD, and AF. The risk of death from either CAD or stroke increases linearly from BP levels as low as 90 mmHg systolic and 75 mmHg diastolic upwards. Evidence suggests that lifetime BP evolution differs in women compared to men, potentially resulting in an increased CVD risk at lower BP thresholds. The SCORE2 algorithm cannot be used for patients with secondary causes and rarer forms of hypertension, such as primary hyperaldosteronism.
- **Cigarette smoking:** A lifetime smoker has a 50% probability of dying due to smoking, and on average will lose 10 years of life. The CVD risk in smokers < 50 years of age is five-fold higher than in non-smokers. Prolonged smoking is more hazardous for women than for men. Worldwide, after high SBP, smoking is the leading risk factor for disability adjusted life-years. Second-hand smoke is associated with an increase in CVD risk. Some smokeless tobacco is also associated with increased risk of CVD.
- **Diabetes mellitus:** Type 1 DM, type 2 DM, and prediabetes are independent risk factors for ASCVD, increasing risk of ASCVD by about two-fold, depending on the population and therapeutic control. Women with type 2 DM appear to have a particularly higher risk for stroke.
- **Adiposity:** Over recent decades, body mass index (BMI) has increased substantially worldwide in children, adolescents, and adults. Mendelian randomization analyses suggest a linear relation between BMI and mortality in non-smokers and a J-shaped relation in ever-smokers. All-cause mortality is lowest at a BMI of 20-25 kg/m² in apparently healthy people, with a J-shaped or U-shaped relation. In HF patients, there is evidence for an obesity paradox, with lower mortality risk in patients with higher BMI. A meta-analysis concluded that both BMI and waist circumference are similarly, strongly, and continuously associated with ASCVD and type 2 DM.

CV disease risk stratification:

- Identifying patients who will benefit most from ASCVD risk factor treatment is central to ASCVD prevention efforts. In general, the higher the absolute CVD risk, the higher the absolute benefit of risk factor treatment.

- Prevention of CVD by treating risk factors is usually done with a lifetime perspective. Lifetime CVD risk can be approximated by clinical experience with clinical criteria such as age, (change in) risk factor levels, risk modifiers, etc. or estimated in apparently healthy people, patients with established ASCVD, and persons with type 2 DM with specific lifetime CVD risk scores. Lifetime benefit from risk factor management can be estimated by combining lifetime risk models with HRs derived from RCTs, meta-analyses of RCTs, or Mendelian randomization studies, which may provide estimates of the effects of longer-term treatment of risk factors. This may in turn increase patient engagement, self-efficacy, and motivation to adhere to lifestyle changes and drug treatment.
- **Risk estimation in apparently healthy people:**
 - Since 2003, the European Guidelines on CVD prevention have recommended use of the Systematic COronary Risk Evaluation (SCORE) system because it is based on large, representative european cohort data sets. The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, in relation to age, sex, smoking habits, total cholesterol level, and SBP. However, CVD morbidity (non-fatal MI, non-fatal stroke) combined with CVD mortality better reflects the total burden of ASCVD.
 - The updated SCORE algorithm -SCORE2- estimates an individual's 10-year risk of fatal and non-fatal CVD events (MI, stroke) in apparently healthy people aged 40-69 years with risk factors that are untreated or have been stable for several years.
 - The SCORE2-OP algorithm estimates 5-year and 10-year fatal and non-fatal CVD events (MI, stroke) adjusted for competing risks in apparently healthy people aged ≥ 70 years.
 - **Several specific considerations apply to CVD risk estimation in older people:**
 - The gradient of the relationship between classical risk factors, such as lipids and BP, with CVD risk attenuates with age.
 - CVD-free survival dissociates from overall survival progressively with increasing age, because risk for non-CVD mortality increases ('competing risk').
 - For these reasons, traditional risk models that do not take into account the competing risk of non-CVD mortality, tend to overestimate the actual 10-year risk of CVD, and hence overestimate the potential benefit of treatment.
 - The SCORE2 charts do not apply to persons with documented CVD or other high-risk conditons such as DM, FH or other genetic or rare lipid or BP disorders (e.g primary hyperaldosteronism), CKD and in preganant women.

- SCORE2 and SCORE2-OP are calibrated to four clusters of countries (low, moderate, high, and very high CVD risk) that are grouped based on national CVD mortality rates published by the WHO.
- **Low-risk countries:** Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the United Kingdom (UK).
- **Moderate-risk countries:** Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden.
- **High-risk countries:** Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey.
- **Very high-risk countries:** Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine, and Uzbekistan.

- **Translating CV disease risk to treatment thresholds:**

While no risk threshold is universally applicable, the intensity of treatment should increase with increasing CVD risk. Across the entire range of CVD risk, the decision to initiate interventions remains a matter of individual consideration and shared decision-making. In general, risk factor treatment recommendations are based on categories of CVD risk ('low-to-moderate', 'high', and 'very high'). The cut-off risk levels for these categories are numerically different for various age groups to avoid under treatment in the young and to avoid overtreatment in older persons. Risk categories do not 'automatically' translate into recommendations for starting drug treatment. In all age groups, consideration of risk modifiers, lifetime CVD risk, treatment benefit, comorbidities, frailty, and patient preferences may further guide treatment decisions. As the 10-year CVD risk thresholds guide treatment decisions and have an impact on healthcare costs and resources, countries or regions may decide on using higher or lower treatment thresholds.

| Table 27-1: CV disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people: | | | | |
|--|--------|------------|-------------|----------|
| Category | Action | < 50 years | 50-69 years | 70 years |

| | | | | |
|----------------------------------|--|------------|---------|-----------|
| Low-to-moderate CVD risk: | risk factor treatment generally not recommended | < 2.5% | < 5% | < 7.5% |
| High CVD risk: | risk factor treatment should be considered | 2.5 - 7.5% | 5 - 10% | 7.5 - 15% |
| Very high CVD risk: | risk factor treatment generally recommended ⁽¹⁾ | ≥ 7.5% | ≥ 10% | ≥ 15% |

(1) *In apparently healthy people ≥ 70 years old, the treatment recommendation for lipid-lowering drugs is Class IIb ('may be considered'). The division of the population into three distinct age groups (< 50, 50-69, and ≥ 70 years) results in a discontinuous increase in risk thresholds for low-to-moderate, high, and very high risk. In reality, age is obviously continuous, and a sensible application of the thresholds in clinical practice would require some flexibility in handling these risk thresholds as patients move towards the next age group, or recently passed the age cut-off.*

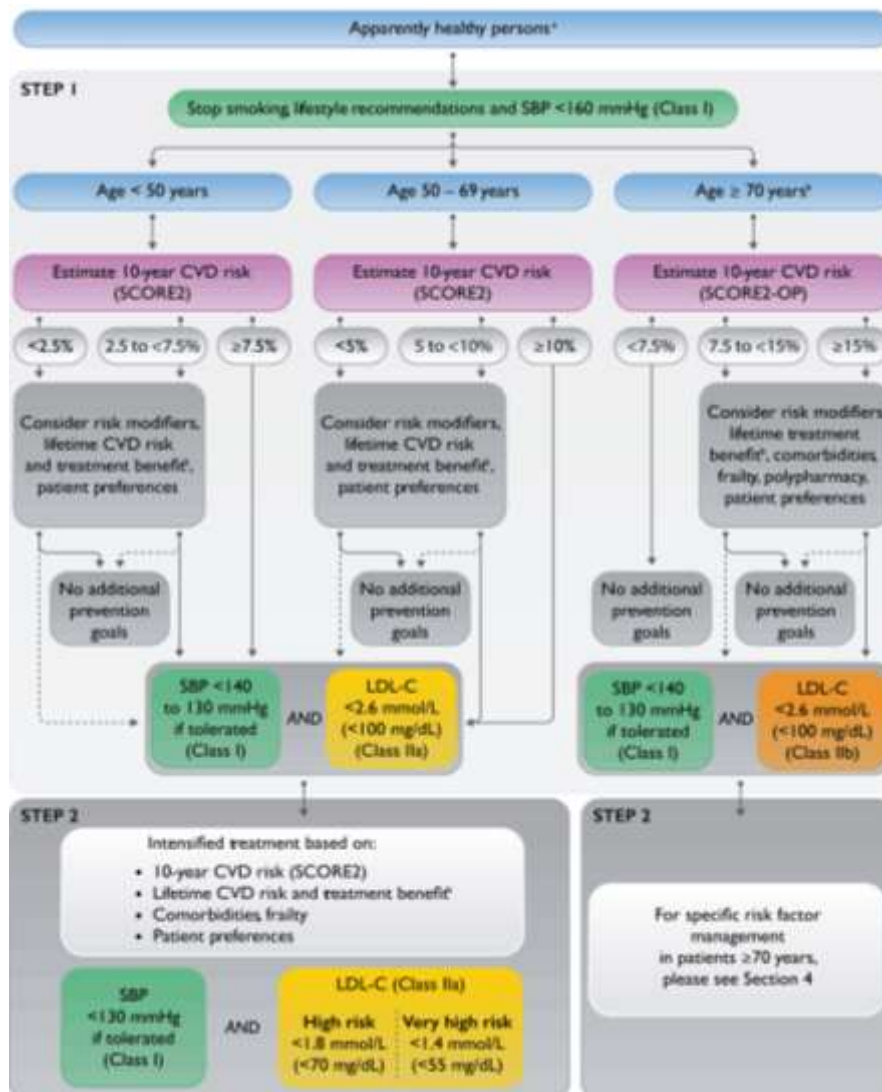


Figure 27-1: Flow chart of cardiovascular disease risk and risk factor treatment in apparently healthy persons. LIFE-CVD = LIFETIME-perspective CardioVascular Disease; SCORE2 = Systematic Coronary Risk Estimation 2; SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons. Solid lines represent default options for the majority of people. Dotted lines represent alternative choices for some, depending on the patient-specific characteristics and conditions indicated in the boxes. Ultimate treatment goals for SBP (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued as indicated. The stepwise approach has to be applied as a whole: after STEP 1, considering proceeding to the intensified goals of STEP 2 is mandatory. **A)** Does not include patients with CVD, DM, CKD, or FH. **B)** The LIFE-CVD model for estimating lifetime CVD risk and treatment benefit is calibrated for low- and moderate risk regions. **Source:** 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.

- **Risk estimation in patients with established ASCVD:**

Patients with clinically established ASCVD are, on average, at very high risk of recurrent CVD events if risk factors are not treated. Therefore, smoking cessation, adoption of a healthy lifestyle, and risk factor treatment is recommended in all patients with clinically established ASCVD (STEP 1). Further intensification of risk factor treatment by aiming at lower treatment goals (STEP 2) is beneficial in most patients and must be considered, taking 10-year CVD risk, comorbidities, lifetime risk and treatment benefit, frailty, and patient preferences into account in a shared decision-making process.

After initial risk factor treatment and the achievement of risk factor treatment goals, the individual residual risk for recurrent CVD varies widely and should be considered. It is evident that patients with a recent ACS or progressive vascular disease, and patients with DM and vascular disease, are all at exceptionally high risk for recurrent CVD events.

The risk of recurrent CVD is influenced mainly by classical risk factors, vascular disease site, and kidney function. Risk stratification tools for secondary prevention include the SMART risk score (for estimating 10-year residual CVD risk in patients with stable ASCVD) and the EUROASPIRE risk model (for estimating 2-year risk of recurrent CVD in patients with stable CAD).

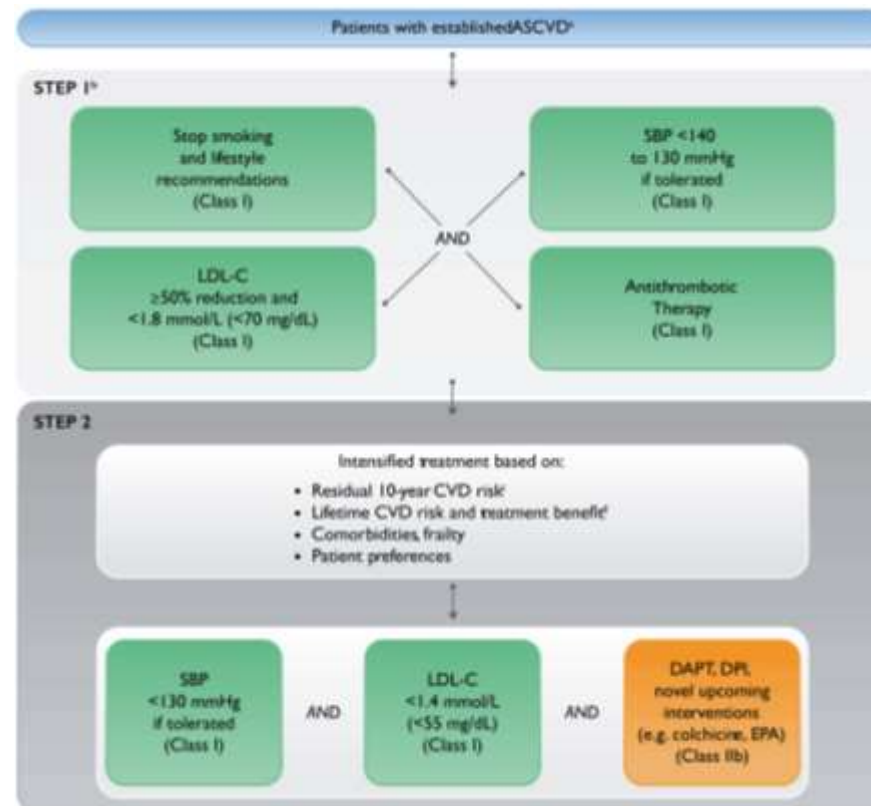


Figure 27-2: Flow chart of cardiovascular risk and risk factor treatment in patients with established atherosclerotic cardiovascular disease. Ultimate treatment goals for SBP (< 130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued as indicated. The stepwise approach has to be applied as a whole: after STEP 1, considering proceeding to the intensified goals of STEP 2 is mandatory. **A)** For patients with DM see DM flow chart. **B)** For patients with recent ACS, these prevention goals are part of participation in CR (Class I/A). **C)** For patients aged ≥ 70 years, a high 10-year risk may be associated with a lower absolute lifetime benefit from treatment due to limited life expectancy. **D)** Lifetime treatment benefit is expressed as extra CVD-free life gained from a certain intervention or treatment intensification. **Source:** 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.

- **Risk estimation in patients with type 2 DM:**

On average, type 2 DM doubles CVD risk and reduces life expectancy by 4-6 years, with absolute risks highest in those with any target organ damage (TOD). Type 2 DM also increases the risk for cardiorenal outcomes, in particular HF and CKD.

Persons with DM with severe TOD can be considered to be at very high CVD risk, similar to people with established CVD. Most others with DM are considered to be at high ASCVD risk. However, an exception can be made for patients with well-controlled short-standing DM (e.g., < 10 years), no evidence of TOD, and no additional ASCVD risk factors, who may be considered as being at moderate CVD risk.

In addition to the semi-quantitative division into three risk categories described above, DM-specific risk models may refine risk estimates and illustrate the impact of treatments. These models generally include duration of DM, HbA1c level, and presence of TOD. Examples are the ADVANCE (predicts 10-year CVD risk), the UKPDS (predicts fatal and non-fatal CVD risk), and the SCORE2-Diabetes (estimate 10-year CVD risk in patients aged ≥ 40 years with T2DM without ASCVD or severe TOD).

- **Risk estimation in persons with type 1 DM:**

People with type 1 DM are at increased CVD risk, and earlier manifestation of type 1 DM relates to more life-years lost in women than men, mostly due to CVD. RRs of CVD are, on average, higher in type 1 vs type 2 DM, due to an average of three to four extra decades of hyperglycemia, and usual risk factors contribute strongly to CVD outcomes in type 1 DM. The absolute risk of CVD events or CVD mortality is highest among those with any evidence of microvascular disease, particularly renal complications, and is strongly influenced by age.

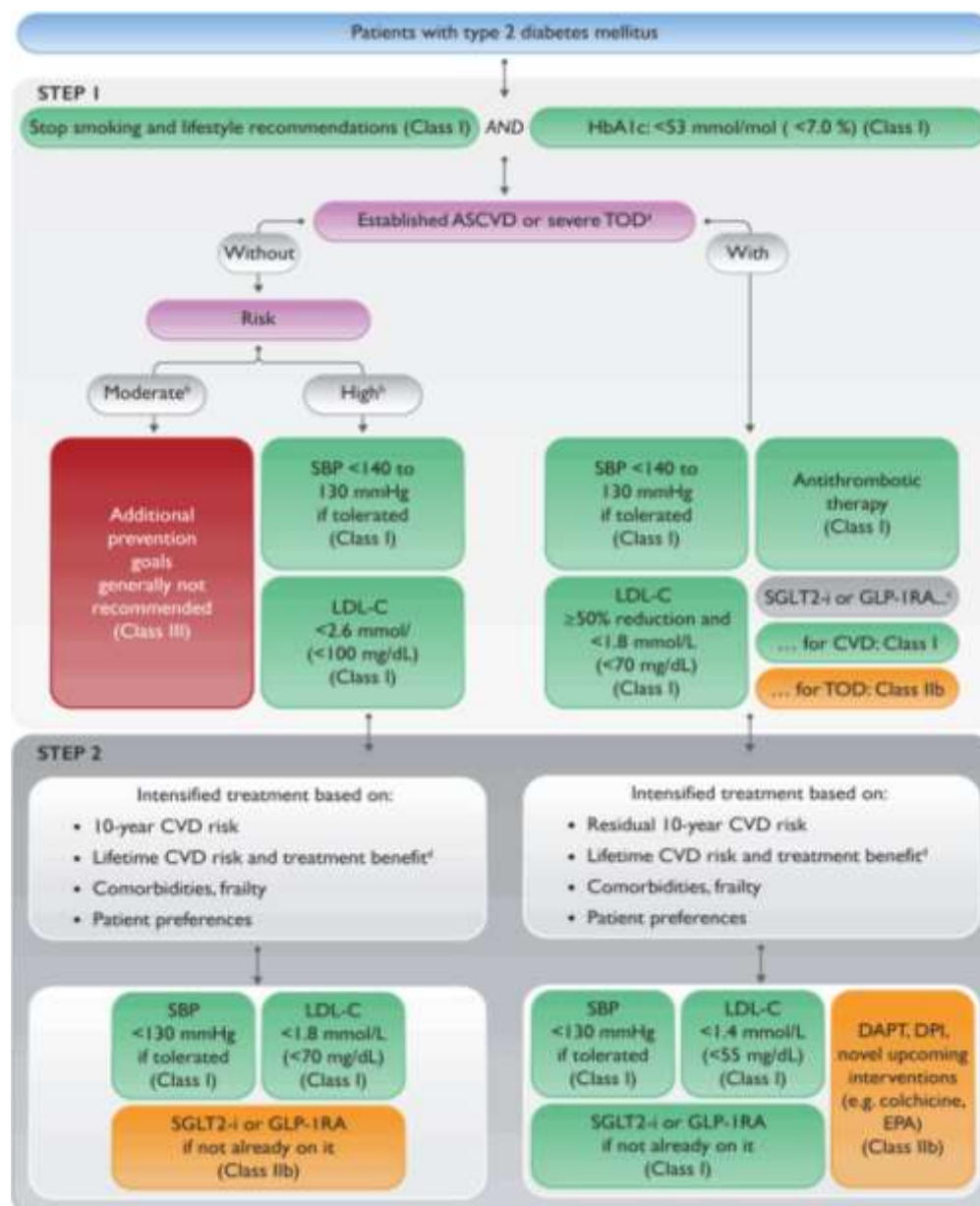


Figure 27-3: Flow chart of cardiovascular risk and risk factor treatment in patients with type 2 diabetes mellitus. Ultimate treatment goals for SBP (<130mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued as indicated. The stepwise approach has to be applied as a whole: after STEP 1, considering proceeding to the intensified goals of STEP 2 is mandatory. ACR = albumin-to-creatinine ratio; ASCVD = atherosclerotic cardiovascular disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; TOD = target organ damage (retinopathy, nephropathy, neuropathy). **A)** Severe TOD is defined as at least one of: eGFR <45 mL/min/1.73 m² irrespective of the presence or absence of albuminuria; eGFR 4659 mL/min/1.73 m² and microalbuminuria (ACR 30-300 mg/g or 330 mg/mmol); proteinuria (ACR > 300 mg/g or > 30 mg/mmol); presence of microvascular disease in at least three different sites (e.g. microalbuminuria plus retinopathy plus neuropathy). **C)** Patients with prevalent HF or CKD are recommended for SGLT2 inhibitor, and patients post stroke are recommended for GLP-1RA treatment. **D)** Lifetime treatment benefit is expressed as extra CVD-free life gained from a certain intervention or treatment intensification. **Source:** 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.

Table 27-2: Patient categories and associated cardiovascular disease risk.

| Patient category | Subgroups | Risk categories | CVD risk and therapy benefit estimation |
|---|---|------------------------|---|
| Apparently healthy persons: | | | |
| Persons without established ASCVD, DM, CKD, Familial Hypercholesterolemia | < 50 years | Low- to high risk | 10-year CVD risk estimation (SCORE2). Lifetime risk and benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of CVD risk and treatment benefits. |
| | 50 - 69 years | Low- to very high-risk | |
| | ≥ 70 years | Low- to very high-risk | |
| Patients with CKD: | | | |
| CKD without DM or ASCVD | Moderate CKD (eGFR 30- 44 and ACR < 30 <u>or</u> eGFR 45-59 and ACR 30 - 300 <u>or</u> eGFR ≥ 60 and ACR > 300) | High-risk | N/A |
| | Severe CKD (eGFR < 30 <u>or</u> eGFR 30-44 and ACR > 30) | Very high-risk | N/A |
| Familial Hypercholesterolemia: | | | |
| Associated with markedly elevated cholesterol levels | N/A | High-risk | N/A |
| Patients with DM: | | | |

| | | | |
|--|--|----------------|--|
| Patients with type 1 DM > 40 years of age may also be classified according to these criteria | Patients with well controlled short-standing DM (e.g. < 10 years), no evidence of TOD and no additional ASCVD risk factors | Moderate risk | N/A |
| | Patients with DM without ASCVD and/or risk criteria. | High-risk | Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model). |
| Patients with type 2 DM | Patients with DM with established ASCVD and/or severe TOD: - eGFR < 45 - eGFR 45-59 and (ACR 30 - 300) - Proteinuria (ACR > 300) - Presence of microvascular disease microalbuminuria + retinopathy + neuropathy) | Very high-risk | |
| Patients with established ASCVD: | | | |
| Documented ASCVD, clinical or unequivocal on imaging. | N/A | Very high-risk | Residual CVD risk estimation after general prevention goals (e.g. 10-year risk with the SMART risk score for |

| | | | |
|---|--|--|---|
| <p>- Documented clinical ASCVD includes: previous ACS, arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD.</p> <p>- Unequivocal on imaging: plaque on coronary angiography or carotid US or on CTA.</p> | | | <p><i>patients with established CVD or 1- or 2-year risk with EUROASPIRE risk score for patients with CHD).</i></p> <p><i>Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. SMART-REACH model; or DIAL model if DM).</i></p> |
|---|--|--|---|

Potential risk modifiers:

Apart from the conventional CVD risk factors included in the risk charts, additional risk factors or types of individual information can also modify calculated risk. Assessment of potential risk modifiers seems particularly relevant if the individual's risk is close to a decision threshold. Assessment of potential risk modifiers seems particularly relevant if the individual's risk is close to a decision threshold. In low-risk or very-high-risk situations, additional information is less likely to alter management decisions.

- **Psychosocial factors:** Psychosocial stress is associated, in a dose-response pattern, with the development and progression of ASCVD, independently of conventional risk factors and sex. Psychosocial stress includes stress symptoms (i.e. symptoms of mental disorders), as well as stressors such as loneliness and critical life events. Conversely, indicators of mental health, such as optimism and a strong sense of purpose, are associated with lower risk.
- **Ethnicity:** Given the considerable variability in ASCVD risk factors between different ethnic groups, no single CVD risk score performs adequately in all groups. Immigrants from South Asia present higher CVD rates independent of other risk factors, whereas adjusted CVD risks appear lower in most other ethnic groups.
- **Imaging:**
 - Coronary artery calcium: Coronary artery calcium (CAC) scoring can reclassify CVD risk upwards and downwards in addition to conventional risk factors, and may thus be considered in men and women with calculated risks around decision thresholds. If CAC is detected, its extent should be compared with what would be expected for a patient of the same sex and age. Higher-than-expected CAC increases the person's calculated risk, whereas absent or lower-than-expected CAC is associated with lower than calculated risk.
 - Contrast computed tomography coronary angiography: 5-year rates of coronary death or MI were reduced when CCTA was used in patients with stable chest pain. The relative reduction in MI was similar in patients with non-cardiac chest pain. Whether CCTA improves risk classification or adds prognostic value over CAC scoring is unknown.
 - Carotid ultrasound: Although the evidence is less extensive than it is for CAC, carotid artery plaque assessment probably also reclassifies CVD risk, and may be considered as a risk modifier in patients at intermediate risk when a CAC score is not feasible. Systematic use of intima-media thickness (IMT) to improve risk assessment is not recommended. Plaque is defined as the

presence of a focal wall thickening that is $\geq 50\%$ greater than the surrounding vessel wall, or as a focal region with an IMT measurement ≥ 1.5 mm that protrudes into the lumen.

- Arterial stiffness: Arterial stiffness is commonly measured using either aortic pulse wave velocity or arterial augmentation index. Studies suggest that arterial stiffness predicts future CVD risk and improves risk classification. However, measurement difficulties and substantial publication bias argue against widespread use.
- Ankle brachial index (ABI): Estimates are that 12-27% of middle-aged individuals have an ABI < 0.9 , around 50-89% of whom do not have typical claudication. An individual patient data meta-analysis concluded that the reclassification potential of ABI was limited, perhaps with the exception of women at intermediate risk.

- **Frailty:**

- Frailty is a multidimensional state, independent of age and multimorbidity, that makes the individual more vulnerable to the effect of stressors. It constitutes a functional risk factor for unfavourable outcomes, including both high CV and non-CV morbidity and mortality.
- Frailty is not the same as ageing and the two should not be confused. The incidence of frailty increases with age, but people of the same chronological age can differ significantly in terms of health status and vitality. 'Biological age' is much more important in the context of clinical status (including frailty features) and hard clinical outcomes (including CVD events). Similarly, although the presence of comorbidities can exacerbate frailty within an individual, frailty is not the same as multimorbidity.
- Frailty screening is indicated in every elderly patient, but should also be performed in every individual regardless of his/her age, when being at risk of accelerated ageing. Most of the tools relate to frail features, including slowness, weakness, low physical activity, exhaustion, and shrinking (e.g. Fried scale, Short Physical Performance Battery, Rockwood Clinical Frailty Scale, handgrip strength, gait speed).
- Frailty is a potential modifier of global CVD risk. The impact of frailty on CVD risk has been demonstrated across the spectrum of ASCVD, with frailty itself rather than classical CVD risk factors predicting both all-cause and CVD mortality in the very old. Importantly, the ability of frailty measures to improve CVD risk prediction has not been formally assessed. Hence, ESC guidelines do not recommend that frailty measures are integrated into formal CVD risk assessment.

- **Family history:** Family history of premature CVD is a simple indicator of CVD risk, reflecting the genetic and environment interplay. However, family history only marginally improves the prediction of CVD risk beyond conventional ASCVD risk factors.
- **Genetics:** For ASCVD, there is, however, a lack of consensus regarding which genes and corresponding single nucleotide polymorphisms should be included, and whether to use risk factor-specific or outcome-specific polygenic risk scores. Polygenic risk scoring has shown some potential to improve ASCVD risk prediction for primary prevention, but the incremental prediction accuracy is relatively modest and needs further evaluation in both men and women.
- **Socioeconomic determinants:** Low socioeconomic status and work stress are independently associated with ASCVD development and prognosis in both sexes. Work stress is determined by job strain (i.e. the combination of high demands and low control at work) and effort-reward imbalance.
- **Environmental exposure:** Environmental exposures with CVD risk modifying potential include air and soil pollution as well as above-threshold noise levels. Evaluating individual cumulative exposure to pollutants and noise remains challenging, but when available, might impact on individual risk assessment.
- **Biomarkers:** Many biomarkers have been suggested to improve risk stratification. Some may be causal [e.g., lipoprotein(a), reflecting a pathogenic lipid fraction], whereas others may reflect underlying mechanisms (e.g., CRP reflecting inflammation) or indicate early cardiac damage (e.g., natriuretic peptides or high-sensitivity cardiac troponin).
- **Body composition:**
 - In observational studies, all-cause mortality is minimal at a BMI of 20-25 kg/m². Mendelian randomization analyses suggest a linear relation between BMI and mortality in never-smokers and a J-shaped relation in ever-smokers.
 - Among those with established ASCVD, the evidence is contradictory. Systematic reviews of patients with ACS or HF have suggested an 'obesity paradox' whereby obesity appears protective. However, this evidence should be interpreted with caution as reverse causality and other biases may be operating.
 - BMI can be measured easily and is used extensively to define categories of body weight. Body fat stored in visceral and other ectopic depots carries a higher risk than subcutaneous fat. Several measures of global and abdominal fat are available, of which waist circumference is the simplest to measure. Two action levels are recommended:

- Waist circumference ≥ 94 cm in men and ≥ 80 cm in women: no further weight gain.
- Waist circumference ≥ 102 cm in men and ≥ 88 cm in women: weight reduction advised.
- A meta-analysis concluded that both BMI and waist circumference are similarly strongly and continuously associated with ASCVD in the elderly and the young and in men and women.

| Table 27-3: ESC Recommendations for CVD risk modifiers: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Stress symptoms and psychosocial stressors modify CVD risk. Assessment of these stressors should be considered.</i> | IIa | B |
| <i>CAC scoring may be considered to improve risk classification around treatment decision thresholds. Plaque detection by carotid ultrasound is an alternative when CAC scoring is unavailable or not feasible.</i> | IIb | B |
| <i>Multiplication of calculated risk by RR for specific ethnic subgroups should be considered ⁽¹⁾.</i> | IIa | B |
| <i>The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended.</i> | III | B |
| <i>Patients at (very) high risk for CVD may be encouraged to try to avoid long-term exposure to regions with high air pollution.</i> | IIb | C |
| <i>In regions where people have long-term exposure to high levels of air pollution, (opportunistic) CVD risk screening programmes may be considered.</i> | IIb | C |

(1) Southern Asian: multiply the risk by 1.3 for Indians and Bangladeshis and 1.7 for Pakistanis; other Asians: multiply the risk by 1.1; Black Caribbean: multiply the risk by 0.85; Black African and Chinese: multiply the risk by 0.7.

CV disease assessment in specific clinical conditions:

Beyond these potential modifiers, specific clinical conditions can influence CVD risk. These clinical conditions often increase the likelihood of CVD, or are associated with poorer clinical prognosis.

- **Chronic kidney disease:**

- CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with health implications. Criteria and markers of kidney damage, especially kidney disease due to DM, are albuminuria [albumin-to-creatinine ratio (ACR) > 30 mg/g] and estimated GFR < 60 mL/min/1.73 m² (using the CKD-EPI Collaboration formula).
- Among persons with CKD, CVD is the leading cause of morbidity and death. Even after adjustment for known CAD risk factors, including DM and hypertension, mortality risk progressively increases with worsening CKD. As GFR declines below 60-75 mL/min/1.73 m², the probability of developing CAD increases linearly, with up to triple the CVD mortality risk when reaching an eGFR of 15 mL/min/1.73 m².

- **Atrial fibrillation:**

- AF appears to be associated with an increased risk of death and of CVD and kidney disease. Furthermore, AF appears to be a stronger risk factor for CVD in women than in men. AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increased risk in men.
- CV risk factor burden and comorbidities, including lifestyle factors and age significantly affect the lifetime risk for AF development. Risk factor and CVD management reduces AF burden. Comorbid conditions need to be actively treated to reduce AF-related mortality and morbidity.

- **Heart failure:**

- HF of ischemic origin constitutes a severe clinical manifestation of ASCVD. Conversely, HF itself (predominantly of ischemic aetiology) increases the risk of CVD events (MI, arrhythmias, ischemic stroke, CV death).
- Asymptomatic LV dysfunction (systolic or/and diastolic dysfunction) as well as overt symptomatic HF [across the spectrum of LVEF] increases the risk of urgent CV hospitalizations (including hospitalizations due to HF worsening) and CV and all-cause deaths.

- The diagnosis of ischemic HF positions individuals at very high-risk CVD risk and justifies recommendations as for secondary prevention therapeutic strategies.
- **Cancer:** In patients with cancer, there is an overlap between cancer and ASCVD risk factors, with shared biological mechanisms and genetic predispositions. Prevention and treatment of these is therefore beneficial in reducing both CVD as well as cancer risk. Owing to recent improvements in clinical outcomes for many patients with cancer, CVD mortality may ultimately exceed those from most forms of cancer recurrence.
- **Chronic obstructive pulmonary disease (COPD):**
 - COPD patients have a two- to three- fold increased risk of CVD compared with age-matched controls when adjusted for tobacco smoking. Patients with mild-to-moderate COPD are 8-10 times more likely to die from ASCVD than respiratory failure, having higher rates of hospitalization and death due to CVD, stroke, and HF.
 - CVD mortality increases by 28%, and the frequency of non-fatal coronary events by 20%, for every 10% decrease in the forced expiratory volume in 1 second (FEV1). Systemic inflammation and oxidative stress caused by COPD promote vascular remodelling, stiffness, and atherosclerosis, and induce a 'procoagulant' state that affects all vasculature types.
 - Cardiac arrhythmias are common and may be due to the hemodynamic effects (pulmonary hypertension, diastolic dysfunction, atrial structural, and electrical remodelling) caused by the disease in combination with autonomic imbalance and abnormal ventricular repolarization.
- **Inflammatory conditions:** Inflammatory conditions increase CVD risk both acutely and over time. The best evidence for chronic inflammation increasing CVD risk is available for rheumatoid arthritis, which increases CVD risk by approximately 50% beyond established risk factors. There is also evidence for an approximately 20% increased CVD risk in patients with active inflammatory bowel disease. In other chronic inflammatory conditions, such as psoriasis and ankylosing spondylitis, CVD risk may also be increased. However, the strength of the evidence is less strong.
- **Infections:**
 - Influenza and acute respiratory tract infection acutely increase CVD risk.

- Infection with HIV is associated with a 19% increased risk of LEAD and CAD beyond that explained by traditional atherosclerotic risk factors. However, for those with sustained CD4 cell counts < 200 cells/mm³, the risk of incident LEAD events is nearly two-fold higher, whereas for those with sustained CD4 cell counts ≥ 500 cells/mm³, there is no excess risk of LEAD events compared with uninfected people.
- **Migraine:** migraine is associated with a two-fold increased risk of ischemic stroke and a 1.5-fold increase in the risk of cardiac ischemic disease. The associations are more evident for migraine with aura.
- **Sleep disorders and obstructive sleep apnea:** Sleep disturbances or abnormal sleep durations are associated with increased CVD risk. Regarding sleep duration, 7 h seems to be optimal for CV health. The most important sleep-related breathing disorder is OSA, which is characterized by repetitive episodes of apnea, each exceeding 10 seconds. Despite the strong associations of OSA with CVD, including hypertension, stroke, HF, CAD, and AF, treatment of OSA by positive airway pressure (PAP) has failed to improve hard CV outcomes in patients with established CVD. Therefore, interventions that include behaviour change (reduction of obesity, alcohol abstinence), sleep hygiene, and stress reduction in addition to PAP are needed.
- **Mental disorders:** All mental disorders (e.g. anxiety disorders, somatoform disorders, substance disorders, personality disorders, mood disorders, and psychotic disorders) are associated with the development of CVD and reduced life expectancy in both sexes. The precise mechanism by which mental disorders increase CVD remains uncertain.
- **Non-alcoholic fatty liver disease:** persons with NAFLD are often overweight or obese, and commonly have abnormal BP, glucose, and lipid levels. Patients with NAFLD should have their CVD risk calculated and be screened for DM.

Table 27-4: ESC Recommendations for cardiovascular disease assessment in specific clinical conditions:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| CKD: | | |
| <i>In all CKD patients, with or without DM, appropriate screening for ASCVD and kidney disease progression, including monitoring changes in albuminuria is recommended.</i> | I | C |
| Cancer: | | |

| | | |
|--|------------|----------|
| <i>It is recommended to monitor cardiac dysfunction using imaging techniques and circulating biomarkers before, periodically during, and after cancer treatment.</i> | I | B |
| <i>Cardioprotection in high-risk patients (those receiving high cumulative doses or combined radiotherapy) receiving anthracycline chemotherapy may be considered for prevention of LV dysfunction.</i> | IIb | B |
| <i>Screening for ASCVD risk factors and optimization of the CVD risk profile is recommended in patients on treatment for cancer.</i> | I | C |
| COPD: | | |
| <i>It is recommended that all COPD patients be investigated for ASCVD and ASCVD risk factors.</i> | I | C |
| Inflammatory conditions: | | |
| <i>Assessment of total CVD risk may be considered in adults with chronic inflammatory conditions.</i> | IIb | B |
| <i>Multiplication of calculated total CVD risk by a factor of 1.5 should be considered in adults with rheumatoid arthritis.</i> | IIa | B |
| Migraine: | | |
| <i>Presence of migraine with aura should be considered in CVD risk assessment.</i> | IIa | B |
| <i>Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.</i> | IIb | B |
| Sleep disorders and OSA: | | |
| <i>In patients with ASCVD, obesity, and hypertension, regular screening for non-restorative sleep is indicated (e.g. by the question: ‘how often have you been bothered by trouble falling or staying asleep, or sleeping too much?’).</i> | I | C |

| | | |
|--|------------|----------|
| <i>If there are significant sleep problems, which are not responding within 4 weeks to sleep hygiene, referral to a specialist is recommended.</i> | I | C |
| Mental disorders: | | |
| <i>It is recommended that mental disorders with either significant functional impairment or decreased use of healthcare systems be considered as influencing total CVD risk.</i> | I | C |
| Sex-specific conditions: | | |
| <i>In women with a history of preeclampsia and/or pregnancy induced hypertension, periodic screening for hypertension and DM should be considered.</i> | IIa | B |
| <i>In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.</i> | IIa | B |
| <i>In women with a history of premature or stillbirth, periodic screening for hypertension and DM may be considered.</i> | IIb | B |
| <i>Assessment of CVD risk should be considered in men with ED.</i> | IIa | C |

Risk factors and interventions at the individual level:

▪ Treatment goals:

| Table 27-5: Treatment goals for different patient categories | | |
|---|--|--|
| Patient category | Prevention goals (STEP 1) | Additional prevention goals (STEP 2) |
| Apparently healthy persons: | | |
| <i>For BP and lipids: initiation of drug treatment based on CVD risk assessment or SBP >160 mmHg</i> | | |
| < 50 years | <ul style="list-style-type: none"> - Stop smoking and lifestyle optimization - SBP < 140 to 130 mmHg if tolerated | <i>- Office BP < 130/80 mmHg if tolerated</i> |

| | | |
|-------------------------------|---|---|
| | -LDL-C < 100 mg/dL) | -LDL-C < 70 mg/dL and ≥ 50% reduction in high-risk patients -LDL-C < 55 mg/dL and ≥ 50% reduction in very-high-risk patients |
| 50 - 69 years | -Stop smoking and lifestyle optimization -SBP <140 to 130 mmHg if tolerated -LDL-C < 100 mg/dL | -Office BP <130/80 mmHg if tolerated -LDL-C < 70 mg/dL and ≥ 50% reduction in high-risk patients -LDL-C < 55 mg/dL and ≥ 50% reduction in very-high-risk patients |
| ≥ 70 years | -Stop smoking and lifestyle optimization -SBP < 140 mmHg if tolerated -LDL-C < 100 mg/dL) | |
| Patients with CKD: | | |
| | -Stop smoking and lifestyle optimization -SBP < 140 to 130 mmHg if tolerated -LDL-C < 100 mg/dL and ≥ 50% LDL-C reduction -Otherwise according to ASCVD and DM history | -LDL-C < 70 mg/dL in high-risk patients and < 55 mg/dL in very-high risk patients |
| Patients with FH: | | |
| | -Stop smoking and lifestyle optimization -SBP < 140 to 130 mmHg if tolerated -LDL-C < 100 mg/dL and ≥ 50% LDL-C reduction -Otherwise according to ASCVD and DM history | -LDL-C < 70 mg/dL in high-risk patients and < 55 mg/dL in very-high risk patients |
| People with type 2 DM: | | |

| | | |
|---|---|--|
| Well-controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors | <i>Stop smoking and lifestyle optimization</i> | |
| Without established ASCVD or severe TOD | <ul style="list-style-type: none"> - <i>Stop smoking and lifestyle optimization</i> - <i>SBP < 140 to 130 mmHg if tolerated</i> - <i>LDL-C < 100 mg/dL</i> - <i>HbA1c < 7.0%</i> | <ul style="list-style-type: none"> - <i>Office BP < 130/80 mmHg if tolerated</i> - <i>LDL-C < 70 mg/dL and ≥ 50% reduction</i> - <i>SGLT2 inhibitor or GLP-1RA</i> |
| With established ASCVD and/or severe TOD | <ul style="list-style-type: none"> - <i>Stop smoking and lifestyle optimisation</i> - <i>SBP < 140 to 130 mmHg if tolerated</i> - <i>LDL-C < 70 mg/dL</i> - <i>HbA1c < 8.0%</i> - <i>SGLT2 inhibitor or GLP1-RA</i> - <i>CVD: antiplatelet therapy</i> | <ul style="list-style-type: none"> - <i>Office BP < 130/80 mmHg if tolerated</i> - <i>LDL-C < 55 mg/dL and ≥ 50% reduction</i> - <i>SGLT2 inhibitor or GLP-1RA if not already on</i> - <i>May consider novel upcoming treatments: DAPT, dual pathway inhibition, colchicine, icosapent ethyl</i> |
| Patients with established ASCVD: | | |
| | <ul style="list-style-type: none"> - <i>Stop smoking and lifestyle optimization</i> - <i>SBP < 140 to 130 mmHg if tolerated</i> - <i>Intensive oral lipid-lowering therapy aiming at ≥ 50%</i> - <i>LDL-C reduction and LDL-C < 70 mg/dL</i> - <i>Antiplatelet therapy</i> | <ul style="list-style-type: none"> - <i>Office BP < 130/80 mmHg if tolerated</i> - <i>LDL-C < 55 mg/dL</i> - <i>May additionally consider novel upcoming treatments: DAPT, dual pathway inhibition, colchicine, icosapent ethyl, etc.</i> |

▪ **Optimizing lifestyle:**

| Table 27-6: ESC Recommendations for lifestyle Optimization: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Physical activity: | | |
| <i>It is recommended for adults of all ages to strive for at least 150-300 min a week of moderate intensity or 75-150 min a week of vigorous intensity aerobic PA, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity.</i> | I | A |
| <i>It is recommended that adults who cannot perform 150 min of moderate-intensity PA a week should stay as active as their abilities and health condition allow.</i> | I | B |
| <i>It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.</i> | I | B |
| <i>Performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce all-cause mortality.</i> | I | B |
| <i>Lifestyle interventions, such as group or individual education, behaviour-change techniques, telephone counselling, and use of consumer-based wearable activity trackers, should be considered to increase PA participation.</i> | Ila | B |
| Nutrition and alcohol: | | |
| <i>A healthy diet is recommended as a cornerstone of CVD prevention in all individuals.</i> | I | A |
| <i>It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.</i> | I | A |
| <i>It is recommended to replace saturated with unsaturated fats to lower the risk of CVD.</i> | I | A |
| <i>It is recommended to reduce salt intake to lower BP and risk of CVD.</i> | I | A |
| <i>It is recommended to choose a more plant-based food pattern, rich in fibre, that includes whole grains, fruits, vegetables, pulses, and nuts.</i> | I | B |
| <i>It is recommended to restrict alcohol consumption to a maximum of 100 g per week.</i> | I | B |

| | | |
|---|------------|----------|
| <i>It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.</i> | I | B |
| <i>It is recommended to restrict free sugar consumption, in particular sugar-sweetened beverages, to a maximum of 10% of energy intake.</i> | I | B |
| Body weight and composition: | | |
| <i>It is recommended that overweight and obese people aim for a reduction in weight to reduce BP, dyslipidemia, and risk of type 2 DM, and thus improve their CVD risk profile.</i> | I | A |
| <i>While a range of diets are effective for weight loss, it is recommended that a healthy diet in regard to CVD risk is maintained over time.</i> | I | A |
| <i>Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.</i> | IIa | B |
| Mental healthcare and psychological intervention: | | |
| <i>Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.</i> | I | C |
| <i>In ASCVD patients with mental disorders, evidence-based mental healthcare and interdisciplinary cooperation are recommended.</i> | I | B |
| <i>ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CV outcomes and reduce stress symptoms.</i> | IIa | B |
| <i>Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.</i> | IIa | B |
| <i>In patients with HF and major depression, SSRIs, SNRIs, and tricyclic antidepressants are not recommended.</i> | III | B |
| Smoking intervention strategies: | | |

| | | |
|--|------------|----------|
| <i>All smoking of tobacco should be stopped, as tobacco use is strongly and independently causal of ASCVD.</i> | I | A |
| <i>In smokers, offering follow-up support, nicotine replacement therapy, varenicline, and bupropion individually or in combination should be considered.</i> | IIa | A |
| <i>Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.</i> | I | B |

Table 27-7: Healthy diet characteristics

| |
|--|
| <i>- Adopt a more plant- and less animal-based food pattern.</i> |
| <i>- Saturated fatty acids should account for < 10% of total energy intake, through replacement by PUFAs, MUFAs, and carbohydrates from whole grains.</i> |
| <i>- Trans unsaturated fatty acids should be minimized as far as possible, with none from processed foods.</i> |
| <i>- < 5 g total salt intake per day</i> |
| <i>- 30-45 g of fibre of per day, preferably from wholegrains</i> |
| <i>- ≥ 200 g of fruit per day (≥ 2-3 servings)</i> |
| <i>- ≥ 200 g of vegetables per day (≥ 2-3 servings)</i> |
| <i>- Red meat should be reduced to a maximum of 350 - 500 g a week, in particular processed meat should be minimized.</i> |
| <i>- Fish is recommended 1-2 times per week, in particular fatty fish.</i> |
| <i>- 30 g unsalted nuts per day</i> |
| <i>- Consumption of alcohol should be limited to a maximum of 100 g per week.</i> |
| <i>- Sugar-sweetened beverages, such as soft drinks and fruit juices, must be discouraged.</i> |
| The Mediterranean diet pattern includes high intakes of fruits, vegetables, pulses, wholegrain products, fish and olive oil, moderate consumption of alcohol and low consumption of red meat, dairy products, and |

saturated fatty acids. Greater adherence to a Mediterranean diet is associated with a reduction in CV incidence or mortality.

N.B: Consumption of more than four cups of coffee per day was associated with a lower risk of CVD in Finnish patients with DM. In a meta-analysis of 18 observational studies, increasing coffee or tea consumption appeared to reduce the risk of DM.

▪ **Management of dyslipidemia:**

| Table 27-8: ESC Recommendations for management of dyslipidemia: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Pharmacological LDL-C lowering for those <70 years: | | |
| <i>It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group.</i> | I | A |
| <i>An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of ≥ 50% from baseline should be considered in apparently healthy persons <70 years at very high risk.</i> | IIa | C |
| <i>An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of ≥ 50% from baseline should be considered in apparently healthy persons <70 years at high risk.</i> | IIa | C |
| <i>In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥ 50% reduction in LDL-C vs. baseline is recommended.</i> | I | A |
| <i>If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.</i> | I | B |
| <i>For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.</i> | IIb | C |

| | | |
|---|--------------------------|----------------------|
| <i>For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.</i> | I | A |
| <i>For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.</i> | I | C |
| <i>If a statin-based regimen is not tolerated at any dosage (even after rechallenge):</i> - ezetimibe should be considered. - a PCSK9 inhibitor added to ezetimibe may be considered. | IIa IIb | B C |
| <i>If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.</i> | IIb | C |
| <i>Statin therapy is not recommended in premenopausal female patients who are considering pregnancy or are not using adequate contraception.</i> | III | C |
| Lipid management in older patients (≥ 70 years): | | |
| <i>Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.</i> | I | A |
| <i>Initiation of statin treatment for primary prevention in older people aged ≥70 may be considered, if at high risk or above.</i> | IIb | B |
| <i>It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions.</i> | I | C |
| Pharmacological treatments of hypertriglyceridaemia: | | |
| <i>Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridemia [triglycerides >2.3 mmol/L (200 mg/dL)].</i> | I | A |
| <i>In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.</i> | IIb | B |

| | | |
|--|------------|----------|
| <i>In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2x2 g/day) may be considered in combination with a statin.</i> | IIb | B |
| Lipid management in patients with diabetes mellitus: | | |
| <i>In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), intensive lipid-lowering therapy, ultimately aiming at ≥ 50% LDL-C reduction and an LDL-C of <1.4 mmol/L (55 mg/dL) is recommended</i> | I | A |
| <i>In patients with type 2 DM > 40 years at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥ 50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.</i> | I | A |
| <i>Statin therapy may be considered in persons aged ≤ 40 years with type 1 or type 2 DM with evidence of TOD and/or an LDL-C level >2.6 mmol/L (100 mg/dL), as long as pregnancy is not being planned.</i> | IIb | C |
| <i>If the LDL-C goal is not reached, statin combination with ezetimibe should be considered.</i> | IIa | C |
| Lipid management in patients with moderate-to-severe CKD: | | |
| <i>The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent, stage 3-5 CKD.</i> | I | A |
| <i>In patients already on statins, ezetimibe, or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.</i> | IIa | C |
| <i>In patients with dialysis-dependent CKD who are free of ASCVD, commencing statin therapy is not recommended.</i> | III | A |

▪ **Management of Hypertension:**

Table 27-9: ESC Recommendations for management of hypertension:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Classification of BP: | | |
| <i>It is recommended that BP should be classified as optimal, normal, high-normal, or grades 1 – 3 hypertension, according to office BP.</i> | I | C |
| Diagnosis of hypertension: | | |
| <i>It is recommended to base the diagnosis of hypertension on: Repeated office BP measurements, on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients) Or Out-of-office BP measurement with ABPM and/ or HBPM when feasible.</i> | I | C |
| Assessment of HMOD: | | |
| <i>To evaluate for the presence of HMOD, measurement of serum creatinine, eGFR, electrolytes, and ACR is recommended for all patients. A 12- lead ECG is recommended for all patients, and echocardiography is recommended for those with ECG abnormalities or signs/symptoms of LV dysfunction. Fundoscopy or retinal imaging is recommended for patients with grades 2 or 3 hypertension and all hypertensive patients with DM.</i> | I | B |
| Thresholds for initiation of drug treatment of hypertension: | | |
| <i>For grade 1 hypertension, treatment initiation based on absolute CVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.</i> | I | C |
| <i>For patients with grade 2 hypertension or higher, drug treatment is recommended.</i> | I | A |
| Office BP treatment targets: | | |
| <i>It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific comorbidities.</i> | I | A |

| | | |
|---|------------|----------|
| <i>In treated patients aged 18-69 years, it is recommended that SBP should ultimately be lowered to a target range of 120 - 130 mmHg in most patients.</i> | I | A |
| <i>In treated patients aged ≥ 70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.</i> | I | A |
| <i>In all treated patients, DBP is recommended to be lowered to <80 mmHg.</i> | I | A |
| Treatment of hypertension: lifestyle interventions: | | |
| <i>Lifestyle interventions are recommended for people with high-normal BP or higher.</i> | I | A |
| Treatment of hypertension: drug treatment: | | |
| <i>It is recommended to initiate antihypertensive treatment with a two-drug combination in most patients, preferably as a single-pill combination. Exceptions are frail older patients and those with low-risk, grade 1 hypertension (particularly if SBP <150 mmHg).</i> | I | B |
| <i>It is recommended that the preferred combinations include a RAS blocker (i.e. an ACE inhibitor or ARB) with a CCB or diuretic, but other combinations of the five major classes can be used (ACE inhibitor, ARB, beta-blocker, CCB, thiazide/thiazide-like diuretic).</i> | I | A |
| <i>It is recommended, if BP remains uncontrolled with a two-drug combination, that treatment be increased to a three-drug combination, usually a RAS blocker with a CCB and a diuretic, preferably as a single-pill combination.</i> | I | A |
| <i>It is recommended, if BP is not controlled by a three-drug combination, that treatment should be increased by the addition of spironolactone, or if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, an alpha-blocker or beta-blocker, or clonidine.</i> | I | B |
| <i>The combination of two RAS blockers is not recommended.</i> | III | A |

▪ **Management of Diabetes mellitus:**

| Table 27-10: ESC Recommendations for the treatment of patients with diabetes mellitus: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Screening: | | |
| <i>When screening for DM in individuals with or without ASCVD, assessment of HbA1c (which can be done non-fasting) or fasting blood glucose should be considered.</i> | IIa | A |
| Lifestyle: | | |
| <i>Lifestyle changes including smoking cessation, a low saturated fat, high-fibre diet, aerobic PA, and strength training are recommended.</i> | I | A |
| <i>Reduction in energy intake is recommended to patients, to help achieve lower body weight or prevent or slow weight gain.</i> | I | B |
| <i>For those motivated to try, considerable weight loss with use of low-calorie diets followed by food reintroduction and weight-maintenance phases early after diagnosis can lead to DM remission and should be considered</i> | IIa | A |
| Glycaemia targets: | | |
| <i>A target HbA1c for the reduction of CVD risk and microvascular complications of DM of <7.0% (53 mmol/mol) is recommended for the majority of adults with either type 1 or type 2 DM.</i> | I | A |
| <i>For patients with a long duration of DM and in old or frail adults, a relaxing of the HbA1c targets (i.e. less stringent) should be considered.</i> | IIa | B |
| <i>A target HbA1c of <6.5% (48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in persons who are not frail and do not have ASCVD.</i> | IIa | B |
| Treatment of hyperglycemia and ASCVD/cardiorenal risks: | | |

| | | |
|--|------------|----------|
| <i>Metformin is recommended as first-line therapy, following evaluation of renal function, in the majority of patients without previous ASCVD, CKD, or HF.</i> | I | B |
| <i>In persons with type 2 DM with ASCVD, metformin should be considered, unless contraindications are present.</i> | IIa | B |
| <i>Avoidance of hypoglycemia and excessive weight gain should be considered.</i> | IIa | B |
| <i>In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes.</i> | I | A |
| <i>In patients with type 2 DM and TOD,c the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits may be considered to reduce future CV and total mortality.</i> | IIb | B |
| <i>In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.</i> | I | A |
| <i>In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.</i> | I | A |
| <i>In patients with type 2 DM but without ASCVD, HF, or CKD, use of an SGLT2 inhibitor or GLP-1RA should be considered based on estimated future risks (e.g. with the ADVANCE risk score or DIAL model) for adverse CVD or cardiorenal outcomes from risk factor profiles.</i> | IIa | B |

▪ **Antithrombotic therapy:**

Antithrombotic therapy in individuals without atherosclerotic disease:

In 2009, a meta-analysis in patients with low CVD risk reported a 12% reduction in ASCVD with aspirin but a significant increase in major bleeding. More contemporary primary prevention trials reported no or little benefit in patients without ASCVD and a consistent increase in bleeding. An updated meta-analysis did not show a reduction in all-cause or CV mortality with aspirin, but did show a lower risk of non-fatal MI and ischemic stroke. Conversely, aspirin was associated with a higher risk of major bleeding, intracranial bleeding, and major GI bleeding, with no difference in the risk of fatal bleeding.

In patients with DM and no evident ASCVD, the ASCEND study reported a 12% risk reduction and a significant increase in major bleeding, but not in fatal or intracranial bleeding.

| Table 27-11: ESC Recommendations for antithrombotic therapy: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Aspirin 75 - 100 mg daily is recommended for secondary prevention of CVD.</i> | I | A |
| <i>Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.</i> | I | B |
| <i>Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.</i> | IIb | A |
| <i>Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.</i> | I | A |
| <i>In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.</i> | IIb | A |
| <i>Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.</i> | III | A |

▪ **Anti-inflammatory therapy:**

Acknowledging that the process of atherosclerosis has inflammatory components has led to the investigation of various anti-inflammatory therapies in recent years.

The first study to examine the effects of reducing inflammation without impacting lipid levels was CANTOS, in which the monoclonal antibody, canakinumab, provided proof-of-concept for anti-inflammatory therapy in high-risk patients. This particular drug was, however, not further developed for this indication because of the risk of fatal infections and high costs.

Methotrexate was the second anti-inflammatory drug studied for this purpose, but was not proven effective in reducing CVD outcomes.

Low-dose colchicine [0.5 mg o.d.] causes a significant reduction in CVD outcomes in patients with a recent AMI (COLCOT and LoDoCo2).

Table 27-12: ESC Recommendations for anti-inflammatory therapy:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| <i>Low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.</i> | IIb | A |

Metabolic syndrome

Definition and risk:

Metabolic syndrome (MS) refers to clustering of several cardiovascular risk factors. The diagnosis is based on having at least three of the following five criteria: **(1)** central obesity (waist circumference > 102 cm in men; and > 88 cm in women); **(2)** elevated triglycerides (≥ 150 mg/dl); **(3)** diminished HDL-C (men < 40 mg/dl; women < 50 mg/dl); **(4)** systemic hypertension (≥ 130 and/or 85 mmHg); and **(5)** elevated fasting glucose (≥ 110 mg/dl).

The WHO requires the demonstration of insulin resistance (diabetes, IFG, or IGT) for diagnosis.

Proinflammatory and prothrombotic states commonly coexist.

The metabolic syndrome is associated with a 2-fold increase in CV outcomes and and diabetes with metabolic syndrome increases CVD risk \approx 5-fold.

Components of metabolic syndrome:

▪ Obesity:

- The rationale for using waist criteria rather than BMI in the diagnosis of obesity in MS arises from data showing that measures of overall obesity are relatively insensitive indicators of the risk for metabolic and cardiovascular complications as compared with measures of central or abdominal obesity. Waist circumference reflects both subcutaneous adipose tissue and abdominal visceral adipose tissue. The visceral adipose tissue is supposed to be the major determinant of metabolic and cardiovascular complications of obesity.

- Obesity should be the primary target of intervention in MS. First line therapy should be weight reduction obtained by lowering caloric intake and reinforcing physical activity (moderate intensity physical activity for a daily minimum of 30 min). Recommendation for diet components include low intake of saturated fats, trans-fats and cholesterol, reduced consumption of simple sugars and increased intake of fruits, vegetables and whole grains.
- A realistic goal is to reduce body weight by 7-10% over 6-12 months.
- **Insulin resistance:**
 - Insulin resistance predicts atherosclerosis and cardiovascular events independently of other risk factors. It generally develops with increasing body fat but in some populations (e.g. south Asians) insulin resistance is common with BMI < 25 kg/m².
 - The mechanisms by which insulin resistance impacts other MS risk factors include:
 - Diversion of excess non-esterified fatty acids from lipid-overloaded insulin resistant muscles to the liver thus promoting fatty liver and atherogenic dyslipidemia.
 - Predisposition to glucose intolerance which can be worsened by increased hepatic gluconeogenesis in the insulin-resistant liver.
 - Blood pressure elevation by a variety of mechanisms.
 - There are two classes of drugs that reduce insulin resistance; metformin and thiazolidinediones. Metformin reduces cardiovascular events and mortality after 11 years of follow up. Among thiazolidinediones, rosiglitazone has been related to an increased risk of MI, whereas pioglitazone decreased the composite endpoint of MI, stroke and death.
- **Atherogenic dyslipidaemia:**
 - Atherogenic dyslipidaemia is often recognized in MS and manifests by raised triglycerides, low HDL, increased remnant lipoproteins, and elevated ApoB containing lipoprotein.
 - Activation of innate immunity and immunity related inflammation have been proposed as potential links between insulin resistance and dyslipidaemia.
 - Statins reduce all ApoB containing lipoproteins and fibrates improve all components of atherogenic dyslipidaemia. A combination of both agents would seem be attractive but may increase the risk of myopathy.

- **High blood pressure:**

- The anti-natriuretic effect of insulin together with its ability to activate the sympathetic nervous system contributes to the development of hypertension. Moreover, both hyperglycaemia and insulin activate the renin angiotensin system which also contributes to raising the blood pressure.
- Lifestyle modification is the cornerstone of management of patients with high normal blood pressure. If hypertension develops, both ACE inhibitors and ARBs carry advantages over other drugs in patients with metabolic syndrome.

- **Pro inflammatory and pro thrombotic states:**

- Chronic subclinical inflammation is part of the MS. There is an elevated level of cytokines and acute phase reactants. High sensitivity CRP > 3 mg/L adds prognostic information about CV risk at all levels of metabolic syndrome, whereas those with levels < 1 mg/L are at substantially lower risk.
- A prothrombotic state in MS is characterized by elevation of fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and possibly other coagulation factors.

Obesity

Definition:

Obesity is defined as body mass index (BMI) ≥ 30 . However, use of BMI can be misleading since it reflects the overall obesity and does not account for body-fat distribution. Likewise, the use of waist circumference can be misleading due to the anthropometric characteristics of the individual subjects.

The regional distribution of body fat is much more important than the adipose tissue mass. Excess accumulation of body fat in the lower part of the body (hips and thigh) is not associated with increased risk of CV disease or type 2 DM. In contrast, excess abdominal fat particularly visceral adipose tissue confers increased risk of metabolic disorders including insulin resistance, atherogenic dyslipidaemia, elevated BP, subtle chronic inflammation and a prothrombotic profile (components of the metabolic syndrome).

Although large waistline alone cannot distinguish between subcutaneous fat from visceral obesity, the simultaneous presence of an increased waistline (≥ 90 cm in men, ≥ 85 cm in women) and high triglyceride levels (≥ 2.0 mmol/L in men, ≥ 1.5 mmol/L in women) is highly predictive of excess visceral adipose tissue.

Cardiovascular and metabolic effects of obesity:

- Intravascular volume is increased.
- Cardiac output is increased mostly due to increased stroke volume. The myocardium adapts by increasing contractile elements resulting in LVH often of the eccentric type.
- Insulin resistance occurs in about 25% of obese individuals. Not all overweight individuals are insulin-resistant and not all insulin-resistant individuals are overweight. A fasting plasma glucose between 110 and 126 mg/dl is predictive of insulin resistance but it is not a sensitive marker, since most subjects with insulin resistance have a fasting glucose < 110 /dl. Insulin resistance typically precedes the development of type 2 diabetes which occurs once relative beta-cell decompensation develops. The latter may be due to inherited abnormalities in beta-cell function or triglyceride accumulation in the beta-cells (lipotoxicity).

The mechanism by which obesity leads to insulin resistance includes:

- Delivery of free fatty acids through the portal vein to the liver with consequent over production of triglyceride-rich lipoproteins, reduction in insulin extraction and increased hepatic glucose production.
- Accumulation of macrophages in visceral fat leading to local inflammation and liberation of adipokines that exacerbate the metabolic disorders mentioned above.
- Obesity is also associated with increased production of leptin as well as leptin resistance. This leads to triglyceride accumulation in various cell types with consequent development of heart failure, insulin resistance, type 2 DM and steatohepatitis.
- Reduced adiponectin production by adipocytes.
- Atherogenic lipoprotein profile which is characterized by: elevated fasting triglycerides, low HDL-C, abundance of small dense LDL-C and elevated apolipoprotein B. This contributes to increased atherosclerosis risk through a variety of associations

including increased thromboxane synthesis, increased postprandial lipemia, increased proteoglycan binding, increased insulin resistance, increased oxidative susceptibility and increased LDL uptake by the arterial wall. Obesity may be rarely associated with severe elevation of triglycerides with values in excess of 1000 mg/dl. This increases the risk of pancreatitis.

- Blood pressure is often high in obese subjects. This is related to sodium and water retention, hyperinsulinemia/insulin resistance and elevation of plasma renin activity and aldosterone levels.
- Adipose tissue is a source of inflammatory mediators including cytokines, tumor necrosis factor alpha and interleukin-6.
- Enhanced thrombosis risk has been linked to elevated fibrinogen, factor VII, factor VIII and von-Willebrand factor.
- Obesity and insulin resistance are associated with endothelial dysfunction with impaired production and response to NO.
- Obesity increases the risk of sudden death possibly as a result of QT prolongation, fatty infiltration of the conduction system and associated sleep apnea.

Treatment:

- Nutrition: An initial target caloric intake of 1200-1500 Kcal/day for most women and 1500-1800 Kcal/day for most men is recommended. A reduction of 500 calories per day may result in a weight loss of 1 pound of fat per week. An initial goal should be a 5-10% weight loss in the first 6 months, and this can be accomplished through caloric restriction, physical activity or both.
- Physical activity: Aim for 30-60 min of moderate activity 7 days per week. Most successful weight-loss programs combine dietary change with routine physical activity.
- Medications: Pharmacotherapy can be considered for those with BMI ≥ 30 kg/m² or 27 kg/m² and at least one comorbid condition or in those with insufficient weight loss with lifestyle interventions.
 - Orlistat, it acts by inhibiting gastric and pancreatic lipase, thus reducing dietary fat absorption by approximately 30% resulting in a modest 3% weight loss. The common GI side effects from fat malabsorption limit its long-term tolerability.
 - Locaserin, a serotonin 5-HT_{2C} receptor antagonist that results in modest weight loss.
 - Phentermine/topiramate, a GABA receptor modulators and norepinephrine releasing agent.

- Naltrexone (opioid antagonist) and Bupropion (dopamine and norepinephrine reuptake inhibitor). They are associated with significant weight reduction (5% and 9% respectively), but they can slightly increase the heart rate or BP because of their sympathetic stimulant effect.
- Liraglutide, a glucagon-like peptide-1 (GLP-1) agonist that was originally developed as an injectable anti-diabetic medication. Side effects include increased risk of thyroid medullary carcinoma and mild increase in heart rate.
- Bariatric surgery: This is usually reserved for patients with severe obesity (BMI > 40 kg/m²), **or** those with BMI > 35 kg/m² and significant complications such as type 2 DM or obstructive sleep apnea. A meta-analysis indicated that patients undergoing bariatric surgery had over 50% lower risks of total, ASCVD, and cancer mortality compared with people of similar weight who did not have surgery.

Types of bariatric surgery:

- Sleeve Gastrectomy is performed by removing approximately 80% of the stomach.
- The Roux-en-Y Gastric Bypass, often called the “gastric bypass”. The name is a French term meaning “in the form of a Y”.
- The Adjustable Gastric Band is a device made of silicone that is placed around the top part of the stomach to limit the amount of food a person can eat.
- The Biliopancreatic Diversion with Duodenal Switch (BPD-DS) begins with creation of a tube-shaped stomach pouch similar to the sleeve gastrectomy. It resembles the gastric bypass, where more of the small intestine is not used.

The mechanism of weight loss may not simply relate to limiting the stomach or absorptive capacity, but rather disrupting the release of ghrelin from the stomach or promoting the release of other peptides from the small bowel, thereby enhancing satiety signaling in the hypothalamus. Hybrid procedures (restrictive and malabsorptive) are more effective than restrictive procedures in terms of the amount of weight loss and the improvement in comorbidities. Bariatric surgery can also improve cardiac geometry as well as systolic and diastolic function of both ventricles.

Cardiac Rehabilitation

Definition:

Coordinated multi-faceted interventions designed to optimize the cardiac patient's physical, psychological and social functioning, in addition to stabilizing, slowing or even reversing the progression of the underlying pathological process, thereby reducing morbidity and mortality.

Goals of cardiac rehabilitation:

- Patient education about the cardiovascular disease.
- Psychological adaptation to the chronic disease process.
- Induction of lifestyle changes with favorable influence on long-term survival.
- Optimized medical therapy of cardiovascular risk factors.

Organization of cardiac rehabilitation programs:

- Rehabilitation programs may be residential (inpatient) or outpatient, with identical objectives. Residential programs are structured to provide more intensive and/or complex interventions to high-risk or unstable patients and thereby facilitate their transition from the hospital phase to a more stable clinical condition that may allow independent life at home. A major limitation of residential programs is the relatively short duration of risk factor management and lifestyle changes. Therefore, these programs should be followed by a long-term outpatient risk reduction with clinical and functional monitoring.
- The cardiac rehabilitation/secondary prevention programs should be delivered under the guidance of a cardiologist who is experienced in exercise testing and exercise training of patients with various forms of cardiovascular diseases. The staff should include physiotherapists or sport teachers, nutrition counselors/dietitians, psychologists/psychiatrists and preferably also a social worker/vocational counselor. Staff members should be well trained in CPR and early defibrillation.
- Easy access to ECG, ergometry, echocardiography, chest radiography and telemetry or Holter monitoring has to be assured.

Phases of cardiac rehabilitation:

Generally cardiac rehabilitation programs are divided into 3 phases:

- **Phase 1:** refers to inpatient programs started soon after the acute event or intervention. These programs are uncommon presently because of the brevity of most hospital stays.
- **Phase 2:** refers to physician-supervised outpatient programs in the post discharge period. Patients in these programs usually exercise 3 times weekly, for a total of 36 sessions over a period of 3-4 months. Alternatives include simple home-based, self-supervised programs.
- **Phase 3:** refers to non-ECG-monitored programs, provided by health clubs and fitness facilities.

A typical exercise training session for cardiac rehabilitation consists of 5-10 minutes of warm-up, followed by at least 20 minutes of aerobic exercise training and 5-10 minutes of cool-down. Some resistance exercise training using light weights or exercise machines should also be performed.

This should include a single set of 8-10 different exercises at a load that allows 8-15 repetitions.

The aerobic exercise-training component is generally performed at 60-70% of VO_{2max} which corresponds to approximately 70-80% of the maximum heart rate. Some patients require lower training intensities.

- **Exercise training:**

- **The value of physical fitness:**

- Physical fitness is different from physical activity. The former refers to the overall exercise ability and is assessed by exercise testing, whereas the latter refers to any body movement required in daily living or as part of exercise program.
- Physical fitness is inversely related to all-cause mortality mostly as a consequence of reduced prevalence of ischemic heart disease. Reduced physical fitness is an independent predictor of mortality equal in importance to smoking or hypertension. An increase of exercise capacity by just one metabolic equivalent (MET) confers a mortality reduction of 12%.
- Traditionally, it has been recommended that a minimum of 1000 Kcal of physical activity energy expenditure should be generated per week to obtain a prognostic benefit. However, it is now clear that there is an inverse association between relative intensity of physical activity and risk of coronary artery disease even in individuals not satisfying the 1000 Kcal/week activity.

- The above considerations, led to the conclusion that men and women should engage in at least 30 to 45 min of moderate physical activity daily on most or preferably all days of the week. Exercise intensity should be at 65-70% of the maximal age-adjusted heart rate. Although there may be a correlation between exercise intensity and mortality reduction, the benefits of vigorous exercise should be weighed against the increased risk of trauma and chronic orthopedic damage.
- In general, the contraindications for regular exercise training are the same as for exercise testing. Resistance training should be avoided in patients with unstable coronary artery disease, decompensated heart failure, LVOT obstruction and retinopathy.
- The initiation of a regular training program in a previously sedentary individual may be associated with adverse cardiovascular events, including sudden cardiac death, acute MI, aortic dissection and cerebrovascular accidents. To minimize hazards, individual risk stratification is necessary prior to regular physical exercise training. High risk individuals including men > 40 years, women > 50 years and those with more than one risk factor for coronary artery disease should undergo maximal exercise test prior to initiation of vigorous exercise training.
- Because of the frequency of orthopedic injuries, walking and swimming are preferable to jogging for primary prevention. The prognostic benefit has so far been established for aerobic endurance (dynamic) training.
- **Assessment of exercise capacity:** In the context of cardiac rehabilitation, exercise testing is a tool not only to prove or exclude myocardial ischemia but also to determine the patient's fitness level prior to initiation of a training program.
- An exercise test is considered maximal when a patient appears to give a genuine maximal effort or when other clinical endpoints are reached. Physiologically maximal exercise is reached when oxygen uptake does not increase any further despite increasing workload. Note that, maximal oxygen uptake is 5 to 11% higher when measured on a treadmill than by a cycle ergometer.
- Despite its undisputed value, maximal exercise test is not without risk. When performed within 4 weeks of an acute MI, mortality rises to 0.03% and the rate of nonfatal MI or need for cardiac resuscitation reaches 0.09%. Sub-maximal exercise tests were developed in order to minimize the patient's risks. However, the diagnostic potential of the test is limited and the test may therefore be falsely negative in patients with significant coronary artery disease.

- In order to assess the patient's exercise tolerance, it is not sufficient to determine the maximal exercise capacity in watts, but it is also desirable to obtain information on subjective exhaustion during the stress test. This is achieved by using the Borg scale of perceived exertion.
- Patients with congestive heart failure are assessed using a six-minute walk test. The patient is instructed to walk as far as possible in 6 min. The test has to be repeated 3 times with resting periods of 15 min between the walks. The longest distance will be recorded. Immediately after the test, heart rate and blood pressure are taken and the perceived exertion is rated according to the Borg scale.
- **Exercise therapy for coronary artery disease:**
 - Clinical effects:
 - Reduction of total mortality (27%)
 - Reduction of cardiac mortality (31%)
 - Improvement of exercise capacity (12 to 32%)
 - Improvement of psychological, functioning and social adaptation
 - No proven effect on return to work.
 - Exercise training increases exercise time until the onset of angina or eliminates angina entirely, by at least 2 mechanisms: reducing the heart rate and systolic blood pressure response to exercise and improving endothelial function.
 - Initiation of therapy:
 - Patients with contraindication to exercise are excluded.
 - Other patients are risk stratified according to the patient's medical history and functional parameters. High risk patients should undergo baseline echocardiography and maximal exercise testing.
 - Sub-maximal strictly aerobic endurance training at 50-80% of the peak oxygen uptake (moderate intensity exercise) is generally regarded as the gold standard. Resistance training may be applied as an additional modality and appears to be safe in low-risk population.
 - Three to four training sessions per week with duration of 30-40 minutes each are necessary to obtain optimal results.

- Mechanisms of improvement:

Training is effective in retarding the progression of atherosclerosis. Only vigorous training programs may be able to actually reverse the process of atherosclerosis.

- Training mobilizes endothelial progenitor cells from the bone marrow which integrate and home into areas of diseased endothelium thereby improving endothelial function or forming entirely new vessels (angiogenesis).
- Increased expression and activity of endothelial nitric oxide synthase and endothelium-dependent vasodilatation.
- Reduction of resting and daytime ambulatory blood pressure (by 3/2.4 and 3.3/3.5 mmHg respectively).
- Reduction in resting sympathetic and increase in vagal tone. Thus, the resting heart rate is reduced and consequently myocardial oxygen consumption decreases. As a result of increased diastolic duration, myocardial perfusion is increased. The ventricular fibrillation threshold is increased as a consequence of lower circulating catecholamine levels.
- Reduction of LDL-C and increase the HDL-C levels.
- Reduction of the incidence of type 2 DM.
- Long term exercise training increases the total vascular bed cross sectional area thereby decreasing the vascular resistance and increasing maximal flow reserve. It also increases platelet cyclic guanosine monophosphate (cGMP) content, and suppresses blood coagulability and viscosity.

- **Exercise therapy for chronic heart failure:**

- Clinical effects:

- Reduction of total mortality (35%)
- Reduction of hospitalization (28%)
- Improvement of symptoms and peak oxygen consumption (20%)
- Small but significant improvement in cardiac size.
- Increase in ejection fraction after prolonged (> 5 years) exercise training.

- Initiation of therapy:

- Patients with chronic heart failure are stratified as a high-risk group for training interventions. However, adverse events are surprisingly low but may include arrhythmias, hypertension and worsening of heart failure. Patients with contraindications to exercise are excluded.
- Training is based on aerobic steady state exercise sessions at 50 to 80% of the peak oxygen consumption for 15 to 30 minutes 3 to 5 times per week. In highly symptomatic patients with very low symptom-free exercise tolerance (<75 watts), shorter training sessions at low intensity (50% of peak oxygen consumption) are indicated. When patients tolerate the initial regimen well, sessions' duration should be prolonged, then training intensity can be increased.
- Resistance exercise may be added to antagonize the wasting syndrome frequently associated with advanced heart failure. Single limb short-term resistance exercise seems to be safe.
- Mechanisms of improvement:
 - Improvement of endothelium dependent vasodilatation with consequent reduction of cardiac afterload and enhanced peripheral perfusion. Increased levels of circulating endothelial progenitor cells which are supposed to be endogenous mediators of vascular regeneration and repair. This may partially explain the improvement in endothelial function after training.
 - Small improvement of cardiac performance.
 - Reduction (25 to 32%) in circulating levels of angiotensin II and aldosterone.
 - Improvement of exercise performance and ventilation dynamics.
 - Improvement of skeletal muscle morphology, metabolism and function. The volume density of cytochrome-C-positive mitochondria is increased permitting an enhanced oxidative phosphorylation.
 - Reversal of inflammatory activation with reduced expression of cytokines and possibly pro-apoptotic factors in skeletal muscle.
- **Exercise therapy after cardiac surgery:**
 - Clinical effects:

- Cardiac surgery is frequently associated with reduced ventilatory capacity in the early postoperative period, pain during respiration and lifting the arms, weight reduction due to the catabolism associated with major trauma and reduction in muscle strength as a consequence of immobilization.
- The objective of cardiac rehabilitation after cardiac surgery is to regain the pre-surgical levels of physical and social functioning and prevent post operative complications such as pneumonia or deep venous thrombosis. After the completion of wound healing, exercise training should be continued to fully recruit the cardiovascular exercise capacity.
- Exercise therapy after cardiac surgery was proven to increase maximal oxygen consumption.
- Initiation of therapy:
 - Severe cardiac arrhythmias, overt cardiac decompensation and paralysis or musculoskeletal disorders prohibit exercise.
 - For patients with stable clinical condition, limited physical exercise is started immediately after surgery in the form of mobilization in the intensive care unit. This should include active/passive exercise, respiratory exercise and walking. Formal exercise training may be initiated when wound healing is adequately advanced. Resistance exercise may be introduced to mitigate the loss of muscle mass and strength.
- **Exercise therapy after PCI:** Cardiac rehabilitation can benefit almost all patients after PCI. It reduces mortality by approximately 45% but does not affect the incidence of recurrent myocardial infarction or repeat revascularization.
- **Exercise therapy in arrhythmia:**
 - Endurance training is both safe and effective in ICD patients when the exercise programme is started under medical supervision for 6 weeks.
 - Pacemakers have different sensors that can adapt heart rate to the patient's physical activity. However, some sensors may require stimuli that are not provided by certain training modes; for example an accelerometer sensor does not adapt to exercising on a stationary bicycle as opposed to training on a treadmill.
- **Exercise therapy in valvular heart disease:** Among patients with valvular heart disease, no symptomatic or prognostic benefit of exercise training has been documented.
- **Exercise therapy in congenital heart disease:**

- Patients with Eisenmenger syndrome are most intolerant to physical activity and only low intensity activities are permitted (≤ 3 METs).
- Patients with repaired or small atrial septal defects without pulmonary hypertension can participate in all sports. Those with significant left-to-right shunting or resting mean pulmonary artery pressure > 20 mmHg are permitted only low-intensity sports.
- Patients with repaired or small VSDs with normal ventricular function, pulmonary artery pressure and no arrhythmias can engage in all sport activities. Those with moderately restrictive VSDs may participate in low intensity isotonic sports.
- Patients with coarctation of the aorta and low gradients (≤ 20 mmHg), systolic blood pressure during exercise < 230 mmHg, no aortic aneurysm and no large collaterals may engage in all sports. Otherwise, they are allowed only low-intensity exercises. After surgical correction, sports (except static exercises) may be started 2-6 months after surgery. In patients with residual gradients > 20 mmHg, aneurysms or aortic wall thinning, only low-intensity exercise is recommended.
- Patients with unrepaired tetralogy of Fallot should avoid all but low-intensity activities. After surgical repair, no exercise restrictions are imposed if there is no residual shunting or right ventricular outflow tract obstruction, normal ventricular size and function and no exercise induced arrhythmias.
- **Dietary counseling:**
 - Subjects following a Mediterranean-style diet had a 50-70% lower risk of recurrent heart disease. The Mediterranean-style diet places emphasis on fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, seeds, olive oil, dairy products, fish and poultry. In addition, wine is consumed in low to moderate amounts.
 - Increasing fibre intake is associated with lower risk of heart disease, possibly as a result of lower LDL-C levels and improved insulin sensitivity. However, this relation did not persist after adjustment for coronary artery disease risk factors.
 - Omega-3 fatty acids exert cardioprotective effects through decreased synthesis of cytokines, stimulation of synthesis of endothelium-derived nitric oxide and having anti-thrombotic action. Subjects who took fish oil had lower rates of death, non fatal MI or stroke than control subjects.

- Antioxidants have been proposed for prevention of coronary events. However no benefit was shown from B-carotene, vitamin E, vitamin C, selenium or multivitamin supplements in reducing the risk of coronary artery disease.
- **Smoking cessation**
 - Smoking cessation reduces mortality and other cardiac events among patients with coronary artery disease by as much as 50%. Treatment should aim at complete cessation and stopping abruptly.
 - Psychological support and nicotine replacement (transdermal patches, chewing gum, nasal sprays, sublingual tablets, oral inhalers) should be implemented.
- **Psychosocial support:**
 - Five specific psychosocial conditions are associated with increased prevalence of coronary artery disease: depression, anxiety, personality traits, social isolation and chronic life stress.
 - The pathophysiological mechanisms underlying this relationship include:
 - Behavioural mechanisms whereby such psychosocial conditions contribute to higher frequency of adverse health behaviour such as poor diet and smoking.
 - Pathophysiological mechanisms such as neuroendocrine, platelet activation and endothelial dysfunction.
 - Although type A behavior characterized by competition, hostility and exaggerated commitment to work continues to receive attention, many studies reveal no correlation between type A behavior and coronary artery disease risk.
 - There is no reliable evidence that proves the benefit of interventions on psychosocial risk factors in primary prevention.
 - For secondary prevention, interventions designed to modify psychosocial risk factors may reduce fatal and nonfatal cardiac events by 30-50% over 22 years. Therefore, it is recommended to routinely include psychosocial components in cardiac rehabilitation programmes such as stress management and counseling in selected cases. Antidepressant drugs have a beneficial effect on event rate and overall clinical wellbeing in post-acute MI patients.
 - Emotional stress can trigger sudden temporary myocardial dysfunction, particularly in women (Takotsubo cardiomyopathy).
- **Sexual problems:**
 - Sexual dysfunction is highly prevalent in patients with coronary artery disease or hypertension.

- Erectile dysfunction in these cases is usually due to the vascular disease itself but may also be secondary to intake of diuretics, beta blockers, ACEIs and other antihypertensive drugs. Treatment of ED includes psychosexual therapy, oral sildenafil or vardenafil, transurethral alprostadil, intracavernous alprostadil, vacuum constriction device, and vascular surgery.
- **Return to work:** The goals of vocational rehabilitation are to evaluate whether returning to work is safe. Up to 80% of patients with uncomplicated MI can return to work.

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Chapter 28:

Hypertension

Definition and classification:

The relationship between BP and CV and renal events is continuous, making the distinction between normotension and hypertension, based on cut-off BP values, somewhat arbitrary. However, in practice, cut-off BP values are used for pragmatic reasons to simplify the diagnosis and decisions about treatment.

Hypertension is defined as office SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

| Table 28-1: Classification of Blood pressure and Definitions of Hypertension grades ⁽¹⁾ : | | | |
|--|-----------------|--------|------------------|
| Category | Systolic (mmHg) | | Diastolic (mmHg) |
| Optimal | < 120 | and | < 80 |
| Normal | 120-129 | and/or | 80-84 |
| High normal | 130-139 | and/or | 85-89 |
| Grade 1 hypertension | 140-159 | and/or | 90-99 |
| Grade 2 hypertension | 160-179 | and/or | 100-109 |
| Grade 3 hypertension | ≥ 180 | and/or | ≥ 110 |
| Isolated systolic hypertension | ≥ 140 | and | < 90 |

(1) Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated. The same classification is used for all ages from 16 years.

Hypertension and total CV risk assessment:

Hypertension rarely occurs in isolation, and often clusters with other CV risk factors such as dyslipidaemia and glucose intolerance. Quantification of total CV risk (i.e. the likelihood of a person developing a CV event over a defined period) is an important part of the risk stratification process for patients with hypertension.

Table 28-2: Classification of hypertension stages according to blood pressure levels, presence of CV risk factors, hypertension-mediated organ damage, or comorbidities:

| Hypertension Staging | Other risk factors | BP (mmHg) grading | | | |
|------------------------------------|---|---|-------------------------------------|---------------------------------------|------------------------------------|
| | | High normal SBP 130-139 DBP 85-89 | Grade 1 SBP 140-159 DBP 90-99 | Grade 2 SBP 160-179 DBP 100-109 | Grade 3 SBP ≥180 Or DBP ≥110 |
| Stage 1 (Uncomplicated) | <i>No other risk factors</i> | <i>Low risk</i> | <i>Low risk</i> | <i>Moderate risk</i> | <i>High risk</i> |
| | <i>1 or 2 risk factors</i> | <i>Low risk</i> | <i>Moderate risk</i> | <i>Moderate to high risk</i> | |
| | <i>≥ 3 risk factors</i> | <i>Low to moderate risk</i> | <i>Moderate to high risk</i> | <i>High risk</i> | |
| Stage 2 (Asymptomatic) | <i>HMOD, CKD grade 3, or DM without organ damage</i> | <i>Moderate to high risk</i> | <i>High risk</i> | <i>High risk</i> | <i>High to very High risk</i> |
| Stage 3 (Established) | <i>Established CVD, CKD grade ≥ 4 or DM with organ damage</i> | <i>Very high risk</i> | | | |

Diurnal variation in blood pressure:

In majority of healthy population, BP is the lowest during nighttime and peaks right after awakening, otherwise known as the “dipper” pattern of diurnal BP variation. This accounts for approximately 10 mmHg of BP variation in dippers. In contrast, “non-dippers” do not exhibit this variation or exhibit it to a lower degree, often due to a disruption in the normal sleep-wake cycle or through effects of pathological processes on neuroendocrine pathways. The normal variation is controlled by clock genes which further regulate neuroendocrine signaling through the hypothalamus. The physiological processes that coincide with sleeping include increased venous return on assuming a supine position leading to greater circulating volume and increased natriuresis. This, along with decreased vascular tone leads to a nighttime fall in BP. The time of awakening corresponds to a natural surge in neurohormones including increase in catecholamines, glucocorticoids, and maximal activity of the RAAS pathway.

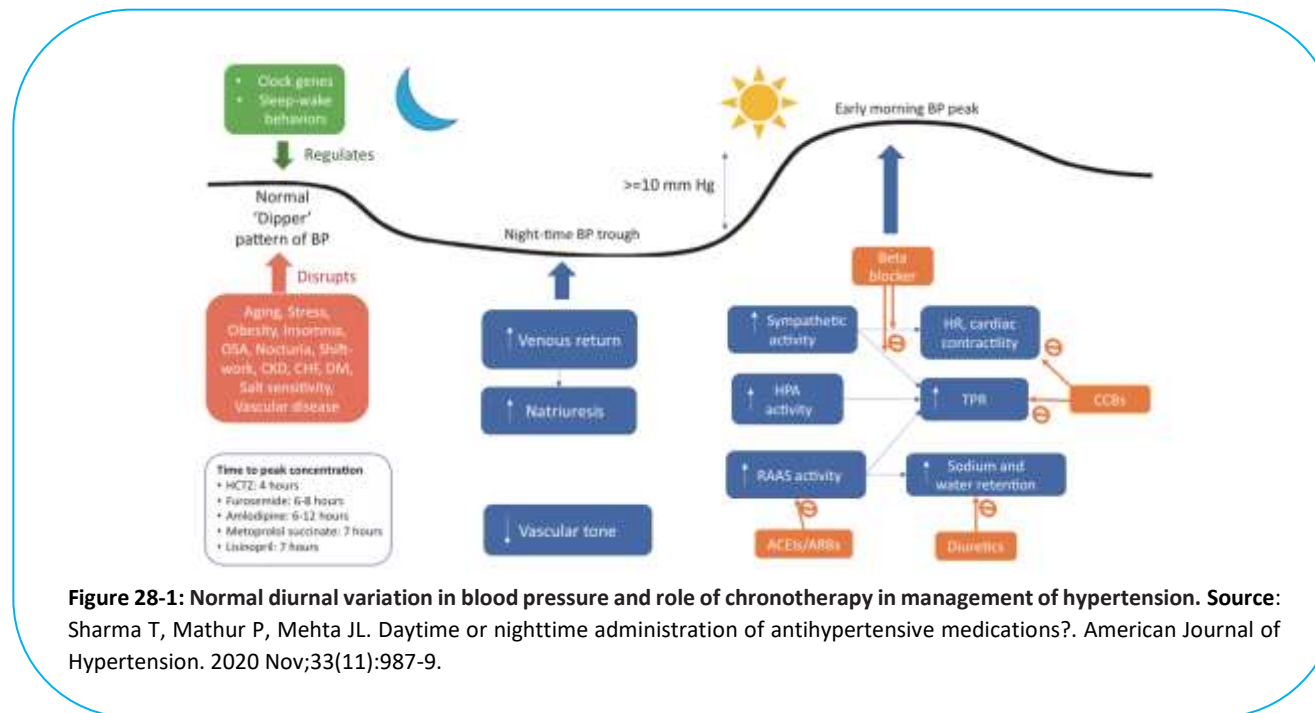


Figure 28-1: Normal diurnal variation in blood pressure and role of chronotherapy in management of hypertension. Source: Sharma T, Mathur P, Mehta JL. Daytime or nighttime administration of antihypertensive medications?. American Journal of Hypertension. 2020 Nov;33(11):987-9.

Diagnostic Aspects:

▪ Blood pressure measurement:

Table 28-3: Definitions of hypertension according to office, ambulatory and home BP levels

| Category | Systolic (mmHg) | | Diastolic (mmHg) |
|------------------------------------|-----------------|--------|------------------|
| Office BP | ≥ 140 | and/or | ≥ 90 |
| Home BP mean | ≥ 135 | and/or | ≥ 85 |
| Ambulatory BP | | | |
| Daytime (or awake) mean | ≥ 135 | and/or | ≥ 85 |
| Night-time (or asleep) mean | ≥ 120 | and/or | ≥ 70 |
| 24 h mean | ≥ 130 | and/or | ≥ 80 |

▪ Conventional office BP measurement:

- Patients should be seated comfortably in a quiet environment for 5 min before BP measurements.
- Three BP measurements should be recorded, 1-2 min apart, and additional measurements only if the first two readings differ by > 10 mmHg. BP is recorded as the average of the last two BP readings.
- Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patients with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.
- Use a standard bladder cuff (12-13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference > 32 cm) and thinner arms, respectively.
- The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependant increases in BP.

- When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.
- Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
- Measure BP 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.
- Record heart rate and use pulse palpation to exclude arrhythmia.
- **Home blood pressure monitoring (HBPM):**
Home BP is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6-7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be performed 1-2 min apart.
- **Ambulatory blood pressure monitoring:**
ABPM provides the average of BP readings over a defined period, usually 24 h. The device is typically programmed to record BP at 15 - 30 min intervals, and average BP values are usually provided for daytime, night-time, and 24 h. A diary of the patient's activities and sleep time can also be recorded.
A minimum of 70% usable BP recordings are required for a valid ABPM measurement session. ABPM values are, on average, lower than office BP values.
- **Screening for the detection of hypertension:**

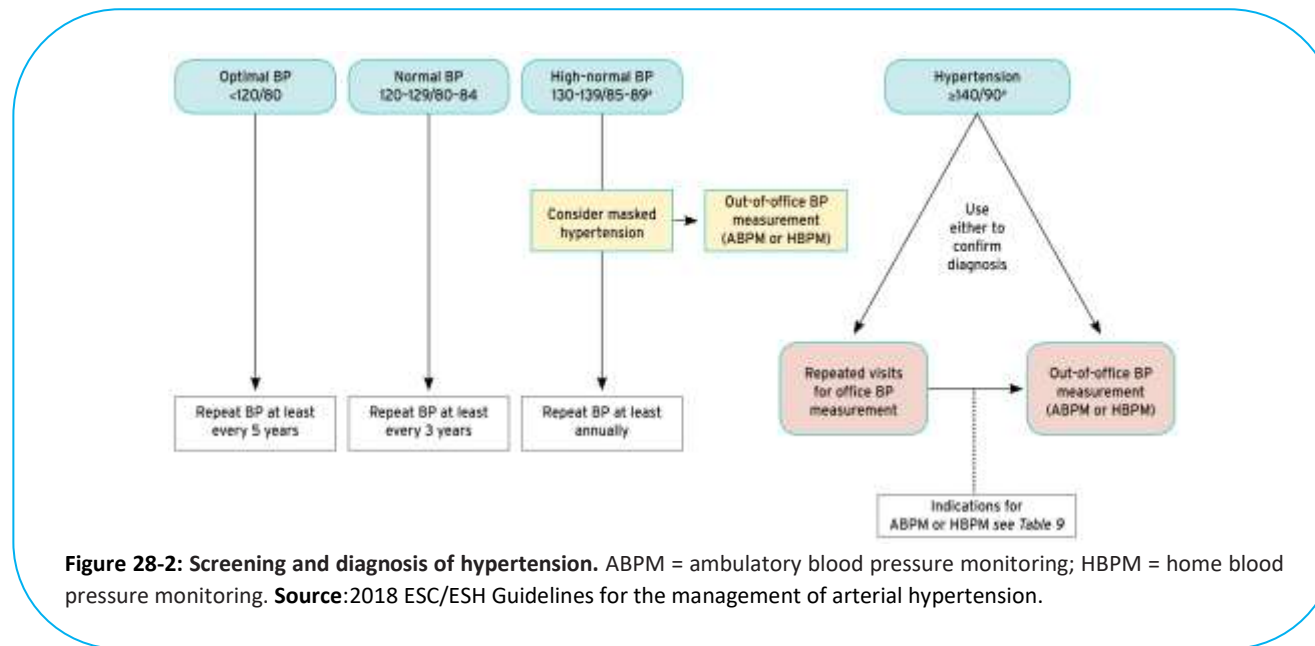


Table 28-4: Clinical indications for Home or Ambulatory BP monitoring:

- Suspected white-coat hypertension, e.g.:
 - Grade I hypertension on office BP measurement
 - Marked office BP elevation without HMOD.
- Suspected masked hypertension, e.g.:
 - High-normal office BP
 - Normal office BP in individuals with HMOD or at high total CV risk
- Postural and post-prandial hypotension in untreated and treated patients
- Evaluation of resistant hypertension
- Evaluation of BP control, especially in treated higher-risk patients.
- Exaggerated BP response to exercise
- When there is considerable variability in the office BP
- Evaluating symptoms consistent with hypotension during treatment

Specific indications for ABPM rather than HBPM:

- Assessment of nocturnal BP values and dipping status (e.g., suspicion of nocturnal hypertension, such as in OSA, CKD, DM, endocrine hypertension, or autonomic dysfunction)

▪ **Confirming the diagnosis of hypertension:**

The diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g., grade 3 hypertension) and there is clear evidence of hypertension-mediated organ damage (HMOD) e.g., hypertensive retinopathy with exudates and hemorrhages, or LVH, or vascular or renal damage.

For all others (i.e. almost all patients), repeat BP measurements at repeat office visits have been a long-standing strategy to confirm a persistent elevation in BP, as well as for the classification of the hypertension status in clinical practice and RCTs.

Table 28-5: ESC recommendations for Blood pressure measurement:

| Recommendations | Class | Level |
|---|--|--|
| <i>Screening programmes for hypertension are recommended. All adults (18 years or older) should have their office BP measured and recorded in their medical file, and be aware of their BP</i> | I | B |
| <ul style="list-style-type: none"> <i>Further BP recording is indicated, at least every 5 years if BP remains optimal.</i> <i>Further BP recording is indicated, at least every 3 years if BP remains normal</i> <i>If BP remains high-normal, further BP recording, at least annually, is recommended.</i> <i>In older patients (> 50 years), more frequent screening of office BP should be considered for each BP category because of the steeper rise in SBP with ageing.</i> | I I I Ila | C C C C |
| <i>It is recommended that office BP should be measured in both arms at least at the first visit because a between-arm SBP difference of > 15 mmHg is suggestive of atheromatous disease and is associated with an increased CV risk.</i> | I | A |
| <i>If a between-arm difference in BP is recorded, then it is recommended that all subsequent BP readings use the arm with the higher BP reading.</i> | I | C |
| <i>It is recommended that the diagnosis of hypertension should be based on:</i> <ul style="list-style-type: none"> <i>○ Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1-2 min apart, and additional measurements should be performed if the first two readings differ by > 10 mmHg. The patient's BP is the average of the last two BP readings. or</i> <i>○ Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.</i> | I I | C C |

| | | |
|--|------------|----------|
| <i>Out-of-office BP (i.e. ABPM or HBPM) is specifically recommended for a number of clinical indications, such as identifying white coat and masked hypertension, quantifying the effects of treatment, and identifying possible causes of side effects (e.g. symptomatic hypotension)</i> | I | A |
| <i>It is recommended that all hypertensive patients undergo pulse palpation at rest to determine heart rate and search for arrhythmias such as AF.</i> | I | C |
| <i>Other BP measures and indices (pulse pressure, BP variability, exercise BP, and central BP) may be considered but are not often used for routine clinical use at present. They may provide useful additional information in some circumstances and are valuable tools for research.</i> | IIb | C |

Hypertension-mediated organ damage (HMOD):

- **Hypertensive cardiac damage:**

- The aetiology of hypertension-induced cardiac damage includes pressure overload, circulating and local factors such as angiotensin II, catecholamine and ETI which promote vascular and myocytes growth, increased connective tissue deposition and collagen cross-linking.
- It is identified by the following features:
 - Atrial (S4) gallop. This is a common and vital clue to the presence of hypertensive heart disease.
 - LVH: The ECG is the most cost-effective way to diagnose and exclude LVH. However, compared with echocardiography, CT or MRI, it is only 10-50% sensitive but at least 80% specific. ECG evidence of LVH is associated with about 3-fold increase in CV events.
 - LVH is associated with reduced diastolic relaxation. Severe diastolic dysfunction may result in "flash pulmonary oedema" despite a normal ejection fraction.

- **Hypertensive vascular damage:** It is identified by the following features:

- Changes in the optic fundi. Three grades are identified.

- Mild hypertensive retinopathy characterized by focal or generalized arteriolar narrowing, arteriolar wall pacification and arteriovenous nicking.
- Moderate hypertensive retinopathy characterized by the above changes plus flame shaped (superficial) or blot shaped (deep) hemorrhages, cotton wool spots (infarcts), hard exudates (fluid leakage), microaneurysms or a combination of these changes.
- Severe hypertensive retinopathy characterized by the above signs plus swelling of the optic disc (papilloedema) due to severe vascular damage and increased permeability of the disk head vessels.
- Ultrasound examination of the carotid arteries with measurement of the intima-media thickness. This has been shown to predict the occurrence of both stroke and MI. The relationship between carotid artery intima-media thickness and cardiovascular events is continuous but a threshold > 0.9 mm can be taken as an estimate of significant alteration.
- Measuring large artery compliance: The increasing interest in systolic BP and pulse pressure as predictors of CV events lead to the development of techniques for determining large artery compliance. Two of these techniques have been well developed, namely the pulse wave-velocity measurement and the augmentation index measurement device. Both are of interest particularly in view of the claim that aortic blood pressure may be better predictive of outcomes and may be differently affected by different antihypertensive drugs.
- Detecting endothelial dysfunction: Endothelial dysfunction or damage is an early marker of CV damage. Circulating markers of endothelial damage (e.g., nitric oxide, endothelins, cytokines and adhesion molecules) may provide simpler tests of endothelial dysfunction.
- **Hypertensive renal damage:**
 - Hypertension is both a cause and complication of CKD and lowering BP slows the progression of renal disease. The systolic BP goal in patients with CKD is < 130 mmHg.
 - Hypertensive renal damage is identified by the following features:
 - Blood urea nitrogen (BUN), serum creatinine, serum electrolytes and urinalysis (particularly for proteinuria) are the only measures of renal function that are currently routinely recommended for evaluation of all hypertensive patients.

- Hyperuricemia, defined as serum urate level above 7 mg/dl is frequently seen in untreated hypertensives and has also been shown to correlate with the existence of nephrosclerosis.
- Microalbuminuria occurs in 5-40% of nondiabetic persons with essential hypertension and is a marker of BP control. Microalbuminuria predicts the development of ischaemic cardiovascular events related to the development of atherosclerosis. BP control with all agents (except dihydropyridine CCBs and central or peripheral sympathetic blockers) reduces albuminuria.
- **Hypertensive brain damage:** is suggested by the following features:
 - History of transient ischemic attack (TIA), stroke, diagnosed with physical finding of focal neurological defects and brain imaging (CT is the standard procedure for diagnosis of stroke, but except for prompt recognition of an intra-cranial hemorrhage, CT is progressively being replaced by MRI techniques).
 - Acute hypertensive encephalopathy is a medical emergency characterized by a very high BP, severe headache and other neurological symptoms (agitation, visual blurring or blindness, drowsiness, confusion, seizures). In this situation, the BP in post capillary venules exceeds the upper limit of cerebrovascular autoregulation, causing pressure-related dilatation with disruption of the blood-brain barrier and focal cerebral edema.
 - SBP is a strong predictor of mild cognitive impairment and frank dementia due to both vascular and Alzheimer's disease.

Clinical Evaluation:

▪ **History:**

○ **Risk factors:**

- Family and personal history of hypertension, CVD, stroke, or renal disease
- Family and personal history of associated risk factors (e.g. familial hypercholesterolaemia)
- Smoking history
- Dietary history and salt intake
- Alcohol consumption
- Lack of physical exercise/sedentary lifestyle

- History of erectile dysfunction
- Sleep history, snoring, sleep apnoea (information also from partner)
- Previous hypertension in pregnancy/pre-eclampsia
- **History and symptoms of HMOD, CVD, stroke, and renal disease:**
 - Brain and eyes: headache, vertigo, syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, dementia (in the elderly)
 - Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, syncope, history of palpitations, arrhythmias (especially AF), heart failure
 - Kidney: thirst, polyuria, nocturia, haematuria, urinary tract infections
 - Peripheral arteries: cold extremities, intermittent claudication, painfree walking distance, pain at rest, peripheral revascularization.
 - Patient or family history of CKD (e.g., polycystic kidney disease)
- **History of possible secondary hypertension:**
 - Young onset of grade 2 or 3 hypertension (< 40 years).
 - Sudden development of hypertension.
 - Rapidly worsening BP in older patients.
 - History of renal/urinary tract disease.
 - Drug abuse or concurrent drugs e.g., steroids, nasal vasoconstrictor, chemotherapy, yohimbine, liquorice
 - Repetitive episodes of sweating, headache, anxiety, or palpitations (suggestive of Pheochromocytoma).
 - History of spontaneous or diuretic-provoked hypokalemia, episodes of muscle weakness, and tetany (suggestive of hyperaldosteronism).
 - Symptoms suggestive of thyroid disease or hyperparathyroidism
 - History of or current pregnancy and oral contraceptive use
 - History of sleep apnea.

○ **Antihypertensive Drug Treatment:**

- Current/past antihypertensive medication including effectiveness and intolerance to previous medications.
- Adherence to therapy.

▪ **Physical examination:**

| Table 28-6: Key steps in physical examination: |
|--|
| Body habitus: |
| <i>Weight and height measured on a calibrated scale, with calculation of BMI</i> |
| <i>Waist circumference</i> |
| Signs of HMOD: |
| <i>Neurological examination and cognitive status</i> |
| <i>Fundoscopy examination for hypertensive retinopathy</i> |
| <i>Palpation and auscultation of heart and carotid arteries</i> |
| <i>Palpation of peripheral arteries</i> |
| <i>Comparison of BP in both arms (at least once)</i> |
| Secondary hypertension: |
| <i>Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma)</i> |
| <i>Kidney palpation for signs of renal enlargement in polycystic kidney disease</i> |
| <i>Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension</i> |
| <i>Comparison of radial with femoral pulse: to detect radio femoral delay in aortic coarctation</i> |
| <i>Signs of Cushing's disease or acromegaly</i> |
| <i>Signs of thyroid disease</i> |

▪ **Routine Workup investigation:**

- Hemoglobin and/or hematocrit
- Fasting blood glucose and glycated HbA1c
- Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol
- Blood triglycerides
- Blood potassium and sodium
- Blood uric acid
- Blood creatinine and eGFR
- Blood liver function tests
- Urine analysis: microscopic examination; urinary protein by dipstick test or, ideally, Albumin:Creat. ratio
- 12-lead ECG.

▪ **Assessment of hypertension-mediated organ damage:**

Table 28-7: ESC recommendations for Clinical evaluation and hypertension-mediated organ damage assessment:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Heart: | | |
| <i>12-lead ECG is recommended for all hypertensive patients.</i> | I | B |
| <i>Echocardiography:</i> | | |
| | I | B |
| | IIb | B |
| Blood vessels: | | |
| <i>Ultrasound examination of the carotid arteries:</i> | I | B |

| | | |
|--|-----|---|
| • May be considered for the detection of asymptomatic atherosclerotic plaques or carotid stenosis in patients with documented vascular disease elsewhere. | IIb | B |
| Measurement of Pulse wave velocity may be considered for measuring arterial stiffness. | IIb | B |
| Measurement of ABI may be considered for the detection of advanced LEAD. | IIb | B |
| Kidney: | | |
| Measurement of serum creatinine and eGFR is recommended in all hypertensive patients. | I | B |
| Measurement of urine albumin:creatinine ratio is recommended in all hypertensive patients. | I | B |
| Renal ultrasound and Doppler examination should be considered in patients with impaired renal function, albuminuria, <u>or</u> for suspected secondary hypertension. | IIa | C |
| Fundoscopy: | | |
| - is recommended in patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes. | I | C |
| - may be considered in other hypertensive patients. | IIb | C |
| Brain: | | |
| In hypertensive patients with neurological symptoms and/or cognitive decline, brain MRI or CT should be considered for detecting brain infarctions, microbleeds, and white matter lesions. | IIa | B |

Table 28-8: Assessment of Hypertension-mediated organ damage:

| Basic screening tests for HMOD | | Indication and interpretation |
|----------------------------------|--|-------------------------------|
| 12-lead ECG | Screen for LVH and other possible cardiac abnormalities, and to document heart rate and cardiac rhythm | |
| Urine Albumin : Creatinine ratio | To detect elevations in albumin excretion indicative of possible renal disease | |
| Blood creatinine and eGFR | To detect possible renal disease | |

| | |
|--|---|
| Fundoscopy | <i>To detect hypertensive retinopathy, especially in patients with grade 2 or 3 hypertension</i> |
| More detailed screening for HMOD | Indication and Interpretation |
| Echocardiography | <i>To evaluate cardiac structure and function, when this information will influence treatment decisions</i> |
| Carotid ultrasound | <i>To determine the presence of carotid plaque or stenosis, particularly in patients with cerebrovascular disease or vascular disease elsewhere</i> |
| Abdominal ultrasound and Doppler studies | <ul style="list-style-type: none"> - <i>To evaluate renal size and structure (e.g. scarring) and exclude renal tract obstruction as possible underlying causes of CKD and hypertension</i> - <i>Evaluate for evidence of aneurysmal dilatation and vascular disease</i> - <i>Examine adrenal glands for evidence of adenoma or pheochromocytoma (CT or MRI preferred for detailed examination).</i> - <i>Renal artery Doppler studies to screen for the presence of renovascular disease, especially in the presence of asymmetric renal size</i> |
| Pulse wave velocity (PWV) | <i>An index of aortic stiffness and underlying arteriosclerosis</i> |
| Ankle Brachial Index (ABI) | <i>Screen for evidence of LEAD</i> |
| Cognitive function testing | <i>To evaluate cognition in patients with symptoms suggestive of cognitive impairment</i> |
| Brain imaging | <i>To evaluate the presence of ischemic or hemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline</i> |

○ECG Definition of LVH:

Table 28-9: Criteria for ECG definition of LVH:

| ECG voltage criteria | Criteria for LVH |
|--|-----------------------------------|
| S in $V_1 + R$ in V_5 (Sokolow-Lyon criterion) | > 35 mm |
| R wave in aVL | ≥ 11 mm |
| S in $V_3 + R$ in aVL (Cornell voltage) | Men > 28 mm and Women > 20 mm |
| Cornell duration product ⁽¹⁾ | > 2440 mm.ms |

○ **Echocardiographic definitions of LVH:**

○ LV geometry can be classified using:

- Relative Wall Thickness (RWT) = $2 \times \text{LV posterior wall thickness} / \text{LVIDD}$. Normal value: ≤ 0.42
- LV Mass Index (LVMI) = $\text{LV mass} / \text{BSA}$. Normal values: ≤ 115 (male) and ≤ 95 (female)

○ LV geometry can be classified into 4 patterns:

- **Normal:** $\text{RWT} \leq 0.42$, normal LVMI
- **Eccentric hypertrophy:** $\text{RWT} \leq 0.42$, increased LVMI
- **Concentric remodelling:** $\text{RWT} > 0.42$, normal LVMI
- **Concentric hypertrophy:** $\text{RWT} > 0.42$, increased LVMI

▪ **Referral to hospital-based care:** Most patients with hypertension will be managed in the primary care setting. However, there are circumstances in which a referral for routine hospital-based evaluation and treatment may be required:

- Suspected secondary hypertension.
- Resistant hypertension
- Patients in whom more detailed assessment of HMOD would influence treatment decisions.
- Patients with sudden onset of hypertension when BP has previously been normal.

(1) Product of cornell voltage \times QRS duration (mm.ms).

- Other clinical circumstances in which the referring doctor feels more specialist evaluation is required.

There are also rarer circumstances in which a patient with hypertension should be referred to hospital for emergency care, which will often require inpatient care.

Treatment of hypertension:

▪ Blood Pressure thresholds for treatment:

- **Age < 80 years:** BP \geq 140/90 mmHg (In patients with CAD or stroke, may be considered if SBP \geq 130)
- **Age \geq 80 years:** BP \geq 160/90 mmHg.

▪ Initiation of BP-lowering treatment at different initial office BP levels:

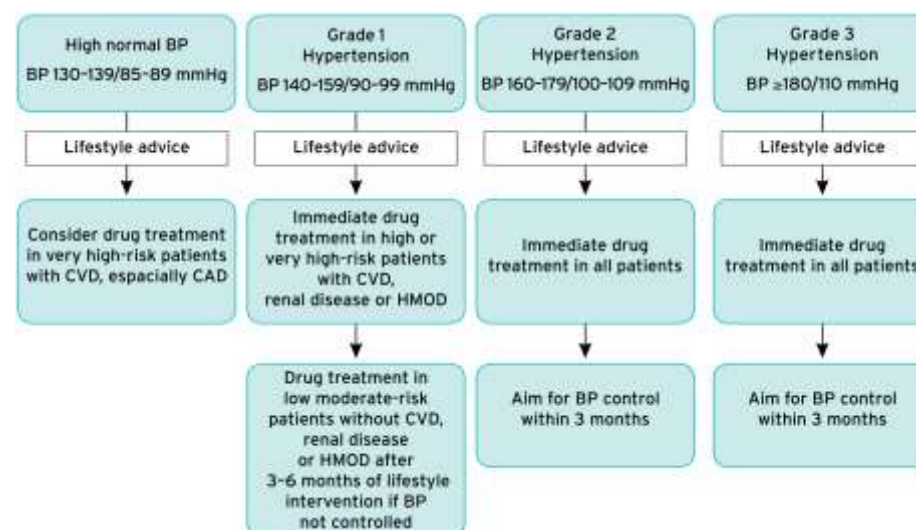


Figure 28-3: Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. Source: 2018 ESC/ESH Guidelines for the management of arterial hypertension.

Table 28-10: ESC recommendations for Initiation of hypertension treatment according to office blood pressure:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneous with the initiation of lifestyle changes.</i> | I | A |
| In patients with grade 1 hypertension: | | |
| - <i>Lifestyle interventions are recommended to determine if this will normalize BP.</i> | IIa | B |
| - <i>In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention ⁽¹⁾.</i> | I | A |
| - <i>In patients with grade 1 hypertension and at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.</i> | I | A |
| <i>In fit older patients with hypertension (even if aged > 80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥ 160 mmHg.</i> | I | A |
| <i>BP-lowering drug treatment and lifestyle intervention are recommended for fit older patients (> 65 years but not > 80 years) when SBP is in the grade 1 range (140-159 mmHg), provided that treatment is well tolerated.</i> | I | A |
| <i>Antihypertensive treatment may also be considered in frail older patients if tolerated.</i> | IIb | B |
| <i>Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, provided that treatment is well tolerated.</i> | III | A |
| In patients with high-normal BP (130-139/85-89 mmHg): | | |
| - <i>Lifestyle changes are recommended.</i> | I | A |
| - <i>Drug treatment may be considered when their CV is very high due to established CVD, especially CAD.</i> | IIb | A |

(1) *In patients with grade 1 hypertension and at low to moderate risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this approach will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range, i.e. the likelihood of achieving BP control with lifestyle intervention alone, and the opportunities for significant lifestyle change in individual patients.*

▪ **Blood pressure treatment targets:**

The level to which BP should be lowered with drug treatment will depend on the patient's age, comorbidities and tolerability of treatment. A target range is recommended to indicate a lower safety boundary beyond which BP should not usually be lowered. Office BP target ranges are summarized below. Corresponding BP targets for home or ambulatory BP are less well validated but an office systolic BP < 130 mmHg probably corresponds to a 24hr ABPM systolic BP of < 125 mmHg and a home average systolic BP of < 130 mmHg.

| Table 28-11: Office blood pressure treatment target range: | | | | | | |
|---|------------------------------------|------------|-------------|-------|-----------|------------------------------------|
| Age group | Office SBP treatment target (mmHg) | | | | | Office DBP treatment target (mmHg) |
| | Hypertension | + Diabetes | +Stroke/TIA | + CAD | + CKD | |
| 18 - 65 years | < 130 | | | | 130 : 139 | 70 : 79 |
| ≥ 65 years | 130 : 139 | | | | | |

| Table 28-12: ESC recommendations for Office blood pressure treatment targets in hypertensive patients: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>It is recommended that the first objective of treatment should be to lower BP to < 140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.</i> | I | A |
| <i>In patients < 65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120-129 mmHg in most patients.</i> | I | A |
| <i>In older patients (aged ≥ 65 years) receiving BP-lowering drugs:</i> - <i>It is recommended that SBP should be targeted to a BP range of 130-139 mmHg.</i> - <i>Close monitoring of adverse effects is recommended.</i> | I | A |

| | | |
|---|-----|---|
| - These BP targets are recommended for patients at any level of CV risk and in patients with and without established CVD. | I | C |
| | I | A |
| A DBP target of < 80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities. | IIa | B |

▪ **Lifestyle interventions:**

| Table 28-13: Adoption of lifestyle changes in patients with hypertension: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Salt restriction to < 5 g per day is recommended. | I | A |
| It is recommended to restrict alcohol consumption to < 14 units/week (for men) and < 8 units/week (for women). | I | A |
| Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended. | I | A |
| Body-weight control is indicated to avoid obesity (BMI > 30 kg/m ² or waist circumference > 102 cm in men and > 88 cm in women), as is aiming at healthy BMI (about 20-25 kg/m ²) and waist circumference values (< 94 cm in men and < 80 cm in women) to reduce BP and CV risk. | I | A |
| Regular aerobic exercise (e.g., at least 30 min of moderate dynamic exercise on 5-7 days per week) is recommended. | I | A |
| Smoking cessation, supportive care, and referral to smoking cessation programs are recommended. | I | B |
| It is recommended to avoid binge drinking. | III | C |

▪ **Pharmacological therapy:**

- The drug treatment algorithm has been developed to provide a simple and pragmatic treatment recommendation, based on a few key recommendations:
- 2. The initiation of treatment in most patients with a single pill combination (SPC) comprising two drugs, to improve the speed, efficiency, and predictability of BP control.
- 3. Preferred two-drug combinations are a RAS blocker with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative when there is a specific indication for a beta-blocker, e.g., angina, post-MI, heart failure, or heart rate control.
- 4. Use monotherapy for low-risk patients with stage 1 hypertension whose SBP is < 150 mmHg, very high-risk patients with high-normal BP, or frail older patients.
- 5. The use of a three-drug SPC comprising a RAS blocker, CCB, and diuretic if BP is not controlled by a two-drug SPC.
- 6. The addition of spironolactone for the treatment of resistant hypertension, unless contraindicated.
- 7. The use of other classes of antihypertensive drugs in the rare circumstances in which BP is not controlled by the above treatments.
- **Timing of antihypertensive:** In most individuals blood pressure tends to be lower while asleep and peaks right after awakening. However, in some individuals this diurnal variation does not exist or is attenuated. These individuals, labeled as “non-dippers,” have greater end-organ damage including greater LVH, silent cerebrovascular disease, and chronic renal damage as compared with “dippers.” Hence, it was advocated that nighttime administration of all antihypertensive agents has shown to improve CV outcomes (Hygia and MAPEC trials). However, the TIME trial showed that antihypertensive therapy can be taken either in the morning or in the evening according to patient preference.

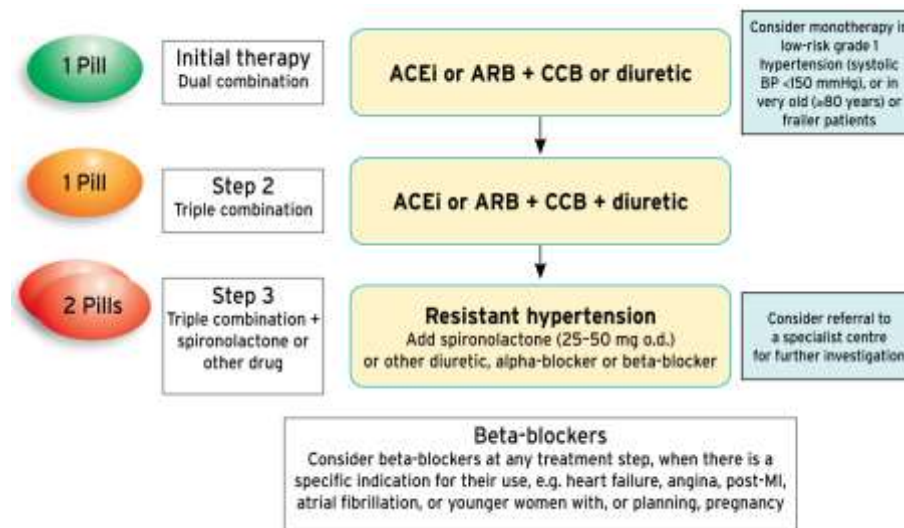


Figure 28-4: Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. **Source:** 2018 ESC/ESH Guidelines for the management of arterial hypertension.

Table 28-14: ESC recommendations for Drug treatment strategy for hypertension:

| Recommendations | Class | Level |
|--|-------|-------|
| <i>Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.</i> | I | A |
| <i>Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.</i> | I | A |

| | | |
|---|------------|----------|
| <i>It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-MI, HF, or heart rate control.</i> | I | A |
| <i>It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg).</i> | I | B |
| <i>It is recommended that if BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.</i> | I | A |
| <i>It is recommended that if BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.</i> | I | B |
| <i>The combination of two RAS blockers is not recommended.</i> | III | A |

Resistant hypertension

Resistant Hypertension is defined as office systolic and diastolic BP exceeding 140 and/or 90 mmHg, respectively, despite the concurrent use of three or more different antihypertensive agents, one of which being a diuretic, and confirmed by ABPM or HBPM.

The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs, which should include a diuretic, typically an ACE inhibitor or an ARB, and a CCB. Pseudo-resistant hypertension and secondary causes of hypertension should also have been excluded.

- **Pseudo-resistant hypertension:** Several possible causes of pseudo-resistant hypertension should be evaluated and ruled out before concluding that the patient has resistant hypertension:

- Poor adherence to prescribed drugs is a frequent cause, occurring in $\leq 50\%$ of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed.
- White-coat phenomenon (in which office BP is elevated but BP is controlled at ABPM or HBPM) is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension.
- Poor office BP measurement technique, including the use of cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP.
- Marked brachial artery calcification, especially in older patients with heavily calcified arteries.
- Clinician inertia, resulting in inadequate doses or unreasonable combinations of BP-lowering drugs.

| Table 28-15: Resistant hypertension | | |
|---|---|---|
| Characteristics of patients with resistant hypertension | Causes of secondary resistant hypertension | Drugs and substances that may cause raised BP |
| Demographics: <ul style="list-style-type: none"> - Older age (esp. > 75 years) - Obesity - More common in black people - Excess dietary sodium intake - High baseline BP and chronicity of uncontrolled hypertension | More common causes: <ul style="list-style-type: none"> - Primary hyperaldosteronism - Atherosclerotic renovascular disease - Sleep apnea - CKD | Prescribed drugs: <ul style="list-style-type: none"> - Oral contraceptives - Sympathomimetic agents (e.g. decongestants in cold drugs) - NSAIDs - Cyclosporin - Erythropoietin - Steroids - Some cancer therapies |
| Concomitant disease: <ul style="list-style-type: none"> - HMOD: LVH and/or CKD | Uncommon causes: <ul style="list-style-type: none"> - Pheochromocytoma | Non-prescription drugs: |

| | | |
|--|---|---|
| <ul style="list-style-type: none"> - Diabetes - Atherosclerotic vascular disease - Aortic stiffening and isolated systolic hypertension | <ul style="list-style-type: none"> - Fibromuscular dysplasia - Aortic coarctation - Cushing's disease - Hyperparathyroidism | <ul style="list-style-type: none"> - Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids) - Excessive liquorice ingestion - Herbal remedies (e.g. ephedra and mahuang) |
|--|---|---|

▪ **Treatment:**

- Effective treatment combines lifestyle changes (especially the reduction of sodium intake).
- Discontinuation of interfering substances.
- Sequential addition of antihypertensive drugs to the initial triple therapy. Ultimately, replacing all current drugs by a simpler treatment regimen using SPC treatment is recommended to reduce pill burden and improve adherence to treatment.
- The most effective strategy seems to be additional diuretic treatment to decrease volume overload, particularly in patients with CKD. BP control may be improved by increasing the dose of the existing diuretic or by switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide). A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is < 30 mL/min.
- Device-based interventions, such as renal denervation, carotid baroreceptors stimulators, and central arteriovenous fistula are still under development.

Table 28-16: ESC recommendations for Resistant hypertension:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <p><i>It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:</i></p> <ul style="list-style-type: none"> - <i>Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACEI or ARB with a CCB and a thiazide/thiazide-type</i> | I | C |

| | | |
|--|----------|----------|
| <p><i>diuretic), fails to lower clinic SBP and DBP values to < 140 mmHg and/or < 90 mmHg, respectively; and</i></p> <ul style="list-style-type: none"> - <i>The inadequate control of BP has been confirmed by ABPM or HBPM; and</i> - <i>After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.</i> | | |
| <p><i>Recommended treatment of resistant hypertension:</i></p> <ul style="list-style-type: none"> - <i>Reinforcement of lifestyle measures, especially sodium restriction.</i> - <i>Addition of low-dose spironolactone ⁽¹⁾ to existing treatment, or</i> - <i>the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride ⁽²⁾, a higher dose thiazide/thiazide-like diuretic, or a loop diuretic.</i> or - <i>the addition of bisoprolol or doxazosin.</i> | I | B |

Secondary hypertension

Patient characteristics that should raise the suspicion of secondary hypertension:

- Younger patients (< 40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood.
- Acute worsening hypertension in patients with previously documented chronically stable normotension.
- Resistant hypertension.
- Severe (grade 3) hypertension or a hypertension emergency.
- Presence of extensive HMOD.
- Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD.

(1) When spironolactone is not tolerated, replace with amiloride or eplerenone. The use of these drugs should be restricted to patients with an eGFR \geq 45 mL/min and serum K \leq 4.5 mmol/L, because of the risk of hyperkalaemia.

(2) A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is < 30 mL/min

- Clinical features suggestive of obstructive sleep apnoea.
- Symptoms suggestive of pheochromocytoma or family history of pheochromocytoma.

Table 28-17: Common causes of secondary hypertension:

| Cause | Prevalence in hypertensive patients | Suggestive symptoms and signs | Screening Investigations |
|--------------------------------------|-------------------------------------|--|--|
| Obstructive sleep apnoea | 5-10% | Snoring; obesity (can be present in non obese); morning headache; daytime somnolence | Epworth score and ambulatory polygraphy |
| Renal parenchymal disease | 2-10% | Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD | Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary albumin:creatinine ratio; renal ultrasound |
| Renovascular disease: | | | |
| Atherosclerotic renovascular disease | 1-10% | Older; widespread atherosclerosis (especially PAD); DM; smoking; recurrent flash pulmonary oedema; abdominal bruit | Duplex renal artery Doppler or CT angiography or MR angiography |
| Fibromuscular dysplasia | | Younger, common in women abdominal bruit | |
| Endocrine causes: | | | |
| Primary Aldosteronism | 5 - 15% | Mostly asymptomatic; muscle weakness (rare) | Plasma aldosterone and renin, and aldosterone:renin ratio; hypokalaemia (in a minority): |

| | | | |
|--|--------|---|---|
| | | | <i>note hypokalaemia can depress aldosterone levels</i> |
| Phaeochromocytoma | < 1% | <i>Episodic symptoms (the 5 'Ps'):</i> <ul style="list-style-type: none"> - <i>Paroxysmal hypertension,</i> - <i>Pounding headache,</i> - <i>Perspiration (sweaty),</i> - <i>Palpitations, and</i> - <i>Pallor;</i> <i>labile BP; BP surges precipitated by drugs (e.g. beta blockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants)</i> | <i>Plasma or 24h urinary fractionated metanephrines</i> |
| Cushing's syndrome | < 1% | <i>Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use</i> | <i>24 h urinary-free cortisol</i> |
| Thyroid disease (hyper- or hypothyroidism) | 1 - 2% | <i>Signs and symptom of hyper- or hypothyroidism</i> | <i>Thyroid function tests</i> |
| Hyperparathyroidism | < 1% | <i>Hypercalcaemia, hypophosphataemia</i> | <i>Parathyroid hormone, Ca²⁺</i> |
| Other causes: | | | |

| | | | |
|--------------------------|------|--|----------------|
| Coarctation of the aorta | < 1% | <i>Usually in children or adolescence; different BP (\geq 20/10 mmHg) between upper-lower extremities and/or between right-left arm and delayed radial femoral pulsation; Low ABI; interscapular ejection murmur; rib notching on chest X-ray</i> | Echocardiogram |
|--------------------------|------|--|----------------|

| Table 28-18: Incidence and typical causes of secondary hypertension according to age: | | |
|---|---------------------------|--|
| Age group | (%) with underlying cause | Typical causes |
| Young children (< 12 years) | 70-85 | <ul style="list-style-type: none"> • Renal parenchymal disease • Coarctation of the aorta • Monogenic disorders |
| Adolescents (12-18 years) | 10-15 | |
| Young adults (19-40 years) | 5-10 | <ul style="list-style-type: none"> • Renal parenchymal disease • Fibromuscular dysplasia (esp. women) • Undiagnosed monogenic disorders |
| Middle-aged adults (41-65 years) | 5-15 | <ul style="list-style-type: none"> • Primary aldosteronism • Obstructive sleep apnoea • Cushing's syndrome • Pheochromocytoma • Renal parenchymal disease • Atherosclerotic renovascular disease |

| | | |
|---|------|---|
| Older adults (> 65 years) | 5-10 | <ul style="list-style-type: none"> • <i>Atherosclerotic renovascular disease</i> • <i>Renal parenchymal disease</i> • <i>Thyroid disease</i> |
|---|------|---|

Table 28-19: Medications and other substances that may increase blood pressure:

| | |
|--|--|
| Oral contraceptive pill | <i>Especially estrogen containing; cause hypertension in 5% of women, usually mild but can be severe</i> |
| Diet pills | <i>For example, phenylpropanolamine and sibutramine</i> |
| Nasal decongestants | <i>For example, phenylephrine hydrochloride and naphazoline hydrochloride</i> |
| Stimulant drugs | <i>Amphetamine, cocaine, and ecstasy; these substances usually cause acute rather than chronic hypertension</i> |
| Liquorice | <i>Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism</i> |
| Immunosuppressive medications | <i>For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP) and steroids</i> |
| Antiangiogenic cancer therapies | <i>Antiangiogenic drugs such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib have been reported to increase BP</i> |
| Other drugs and substances | <i>Anabolic steroids, erythropoietin, NSAIDs, and herbal remedies (e.g. ephedra and ma huang)</i> |

Hypertension urgencies and emergencies

Hypertension emergencies are situations in which severe hypertension (grade 3) is associated with acute HMOD, which is often life-threatening and requires immediate but careful intervention to lower BP, usually with intravenous therapy.

The rate and magnitude of an increase in BP may be at least as important as the absolute level of BP in determining the magnitude of organ injury. Typical presentations of a hypertension emergency are:

- **Patients with malignant hypertension**, characterized by severe hypertension (usually grade 3) associated with fundoscopic changes (flame haemorrhages and/or papilloedema), microangiopathy, and disseminated intravascular coagulation, and can be associated with encephalopathy (in about 15% of cases), acute heart failure, and acute deterioration in renal function. The hallmark of this condition is small artery fibrinoid necrosis in the kidney, retina, and brain. The term 'malignant' reflects the very poor prognosis.
- **Patients with severe hypertension** associated with other clinical conditions who are likely to require an urgent reduction of BP, e.g., acute aortic dissection, acute myocardial ischaemia, or acute heart failure.
- **Patients with sudden severe hypertension** due to pheochromocytoma, associated with organ damage.
- **Pregnant women with severe hypertension or preeclampsia.**

“**Hypertension urgency**” has also been used to describe severe hypertension in patients presenting to the emergency department in whom there is no clinical evidence of acute HMOD. Whilst these patients require BP reduction, they do not usually require admission to hospital, and BP reduction is best achieved with oral medication according to the drug treatment algorithm. However, these patients will require urgent outpatient review to ensure that their BP is coming under control.

▪ Diagnostic workup:

○ **Common tests for all potential causes:**

- Fundoscopy is a critical part of the diagnostic workup.
- 12-lead ECG
- Haemoglobin, platelet count, fibrinogen

- Creatinine, eGFR, electrolytes, LDH, haptoglobin
 - Urine albumin:creatinine ratio, urine microscopy for red cells, leucocytes, casts.
 - Pregnancy test in women of child-bearing age
- **Specific tests by indication:**
- Troponin, CK-MB (in suspected cardiac involvement, e.g., acute chest pain or acute HF) and NT-proBNP
 - Chest X-ray (fluid overload)
 - Echocardiography (aortic dissection, heart failure, or ischaemia)
 - CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
 - CT or MRI brain (nervous system involvement)
 - Renal ultrasound (renal impairment or suspected renal artery stenosis).
 - Urine drug screen (suspected methamphetamine or cocaine use).

▪ **Treatment:**

| Table 28-20: Hypertensive emergencies requiring immediate BP lowering with I.V drug therapy: | | | |
|--|--|----------------------------------|-----------------------------------|
| Clinical presentation | Timeline and target for BP reduction | First-line treatment | Alternative |
| Malignant hypertension ± acute renal failure | <i>Several hours Reduce MAP by 20-25%</i> | <i>Labetalol Nicardipine</i> | <i>Nitroprusside Urapidil</i> |
| Hypertensive encephalopathy | <i>Immediately reduce MAP by 20-25%</i> | <i>Labetalol, nicardipine</i> | <i>Nitroprusside</i> |
| Acute coronary event | <i>Immediately reduce SBP to < 140 mmHg</i> | <i>Nitroglycerine, labetalol</i> | <i>Urapidil</i> |

| | | | |
|--|--|---|--------------------------------------|
| Acut pulmonary oedema | <i>Immediately reduce SBP to < 140 mmHg</i> | <i>Nitroprusside or nitroglycerine (with loop diuretic)</i> | <i>Urapidil (with loop diuretic)</i> |
| Acute aortic dissection | <i>Immediately reduce SBP to < 120 mmHg AND heart rate to < 60 bpm</i> | <i>Esmolol and nitroprusside or nitroglycerine or nicardipine</i> | <i>Labetalol OR metoprolol</i> |
| Eclampsia and severe preeclampsia/HELLP | <i>Immediately reduce SBP to < 160 mmHg AND DBP to < 105 mmHg</i> | <i>Labetalol or nicardipine and magnesium sulfate</i> | <i>Consider delivery</i> |

Table 28-21: Drug types, doses, and characteristics for treatment of hypertension emergencies

| Drug | Onset of action | Duration of action | Dose | Contraindications | Adverse effects |
|-------------------|------------------------|---------------------------|---|---|--|
| Esmolol | 1-2 min | 10–30 min | <i>Bolus: 0.5–1 mg/kg; Maintenance: 50–300mg/kg/min</i> | <i>Second or third-degree AV block, systolic heart failure, asthma, bradycardia</i> | <i>Bradycardia</i> |
| Metoprolol | 1-2 min | 5–8 h | <i>15 mg i.v., usually given as 5 mg i.v., and repeated every 5 min as needed</i> | | |
| Labetalol | 5-10 min | 3–6 h | <i>0.25–0.5 mg/kg; 2–4 mg/min until goal BP is reached, thereafter 5–20 mg/h</i> | | <i>Bronchoconstriction, foetal bradycardia</i> |
| Fenoldopam | 5-15 min | 30–60 min | <i>0.1 mg/kg/min, increase every 15 min</i> | <i>Caution in glaucoma</i> | |

| | | | | | |
|--|-----------|-----------|--|--|-------------------------------------|
| (Dopamine 1 receptor agonist) | | | <i>until goal BP is reached</i> | | |
| Clevidipine (DHB-CCB) | 2-3 min | 5–15 min | <i>2 mg/h, increase every 2 min with 2 mg/h until goal BP</i> | | <i>Headache, reflex tachycardia</i> |
| Nicardipine | 5-15 min | 30–40 min | <i>5–15 mg/h as continuous infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until goal BP, thereafter decrease to 3 mg/h</i> | <i>Liver failure</i> | <i>Headache, reflex tachycardia</i> |
| Nitroglycerine | 1-5 min | 3–5 min | <i>5–200 mg/min, 5mg/min increase every 5 min</i> | | <i>Headache, reflex tachycardia</i> |
| Nitroprusside | Immediate | 1–2 min | <i>0.3–10 mg/kg/min, increase by 0.5 mg/kg/min every 5 min until goal BP</i> | <i>Liver/kidney failure (relative)</i> | <i>Cyanide intoxication</i> |
| Enalaprilat Active metabolite of enalapril | 5-15 min | 4–6 h | <i>0.62–1.25 mg i.v.</i> | <i>History of angioedema</i> | |

| | | | | | |
|--|---------|-----------|---|--|---------------------------------------|
| Urapidil Alpha1 antagonist and central serotonin agonist | 3-5 min | 4–6 h | <i>Bolus: 12.5–25 mg</i> <i>Maintenance: 5-40 mg/h</i> | | |
| Clonidine Alpha2 agonist | 30 min | 4–6 h | <i>150-300 mg i.v. over 5–10 min</i> | | <i>Sedation, rebound hypertension</i> |
| Phentolamine | 1–2 min | 10–30 min | <i>Bolus: 0.5-1 mg/kg OR 50-300 mcg/kg/min</i> | | <i>Tachyarrhythmias, chest pain</i> |

White coat and masked hypertension

White-coat hypertension refers to the untreated condition in which BP is elevated in the office, but is normal when measured by ABPM, HBPM, or both. Conversely, '**masked hypertension**' refers to untreated patients in whom the BP is normal in the office, but is elevated when measured by HBPM or ABPM.

The term 'true normotension' is used when both office and out-of-office BP measurements are normal, and 'sustained hypertension' is used when both are abnormal.

In white-coat hypertension, the difference between the higher office and the lower out-of-office BP is referred to as the 'white-coat effect', and is believed to mainly reflect the pressor response to an alerting reaction elicited by office BP measurements by a doctor or a nurse, although other factors are probably also involved.

| Table 28-22: ESC recommendations for Management of white-coat and masked hypertension: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Management of white-coat hypertension: | | |
| <i>In white-coat hypertensive patients, it is recommended to implement lifestyle changes aimed at reducing CV risk as well as regular follow-up with periodic out-of-office BP monitoring.</i> | I | C |
| <i>In patients with white-coat hypertension:</i> | | |
| - Drug treatment may be considered in people with evidence of HMOD <u>or</u> in whom CV risk is high or very high. | IIb | C |
| - Routine drug treatment is not indicated. | III | C |
| Management of masked hypertension: | | |
| <i>In masked hypertension, lifestyle changes are recommended to reduce CV risk, with regular follow-up, including periodic out-of office BP monitoring.</i> | I | C |
| <i>Antihypertensive drug treatment should be considered in masked hypertension to normalize the out-of-office BP, based on the prognostic importance of out-of-office BP elevation.</i> | IIa | C |
| <i>Antihypertensive drug uptitration should be considered in treated patients whose outof-office BP is not controlled (i.e., masked uncontrolled hypertension), because of the high CV risk of these patients.</i> | IIa | C |

Nocturnal hypertension

- **Definition:** Nocturnal hypertension is defined as average night-time BP $\geq 120/70$ mmHg. If office and morning home BP is $< 130/80$ mmHg, it is called “masked nocturnal hypertension”.
- The night-time BP is measured by ABPM. The number of night-time BP measurements required may be ≥ 6 .

- The night-time systolic BP dipping (%)= $1 - (\text{average night-time SBP} / \text{average daytime SBP}) \times 100$
- Based on this percentage, the following 4 night-time BP dipping patterns are defined: extreme dipper (> 20%); dipper (10-20%); non-dipper (0-10%); riser ($\leq 0\%$).
- **Associated Conditions:**
There are many conditions associated with nocturnal hypertension. DM, CKD, and OSA are the 3 diseases most frequently associated with nocturnal hypertension.
- **Pathophysiology:**
Advanced structural vascular disease (increased vascular resistance and arterial stiffness), increase in salt sensitivity (increased by renal dysfunction, sympathetic hyperactivity, and RAAS activation) and high-salt diet are the main causes of nocturnal hypertension, especially in patients with an increase in basal night-time BP.
- **Management:**
 - First step is to achieve the ideal target of morning home systolic BP < 130/80 mmHg.
 - Second step:
 - In patients with increased circulating volume: Salt restriction, diuretics, ARNI, and SGLT2 inhibitors.
 - In patients with advanced vascular disease: CCB monotherapy or CCB + RAAS inhibitor.
 - In patients with OSA: CPAP, Sympatholytic treatment using β -/ α -blockers and renal denervation.
 - In patients with sleep disorders: Hypnotics, such as melatonin, melatonin receptor agonists, and orexin receptor antagonists, might be preferable.

Hypertension in specific population:

▪ Hypertension in different ethnic groups:

Table 28-23: ESC recommendations for Hypertension in different ethnic groups:

Recommendations

Class Level

| | | |
|---|------------|----------|
| <i>It is recommended that a two-drug combination, usually as an SPC, is used as initial therapy for most black patients.</i> | I | C |
| <i>In black patients, initial antihypertensive treatment should include a diuretic or a CCB, either in combination or with a RAS blocker.</i> | I | B |
| <i>In other ethnic groups, BP-lowering treatment may be based on the core treatment algorithm.</i> | IIb | C |

▪ **Hypertension in diabetes mellitus:**

| Table 28-24: ESC recommendations for Treatment strategies in hypertensive people with diabetes: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>Antihypertensive drug treatment is recommended for people with diabetes when office BP is $\geq 140/90$ mmHg.</i> | I | A |
| <i>In people with diabetes receiving BP-lowering drugs it is recommended:</i> | | |
| - <i>To target SBP to 130 mmHg and < 130 mmHg if tolerated, but not < 120 mmHg.</i> | I | A |
| - <i>In older people (aged ≥ 65 years aged), to target to an SBP range of 130–139 mmHg.</i> | I | A |
| - <i>To target the DBP to < 80 mmHg, but not < 70 mmHg.</i> | I | C |
| <i>It is recommended to initiate treatment with a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic ⁽¹⁾.</i> | I | A |
| <i>Simultaneous administration of two RAS blockers, e.g. an ACE inhibitor and ARB, is not indicated.</i> | III | A |

(1) When eGFR < 30 mL/min/1.73 m², avoid thiazide/thiazide-like diuretics and consider using a loop diuretic when a diuretic is required.

▪ **Hypertension in CKD:**

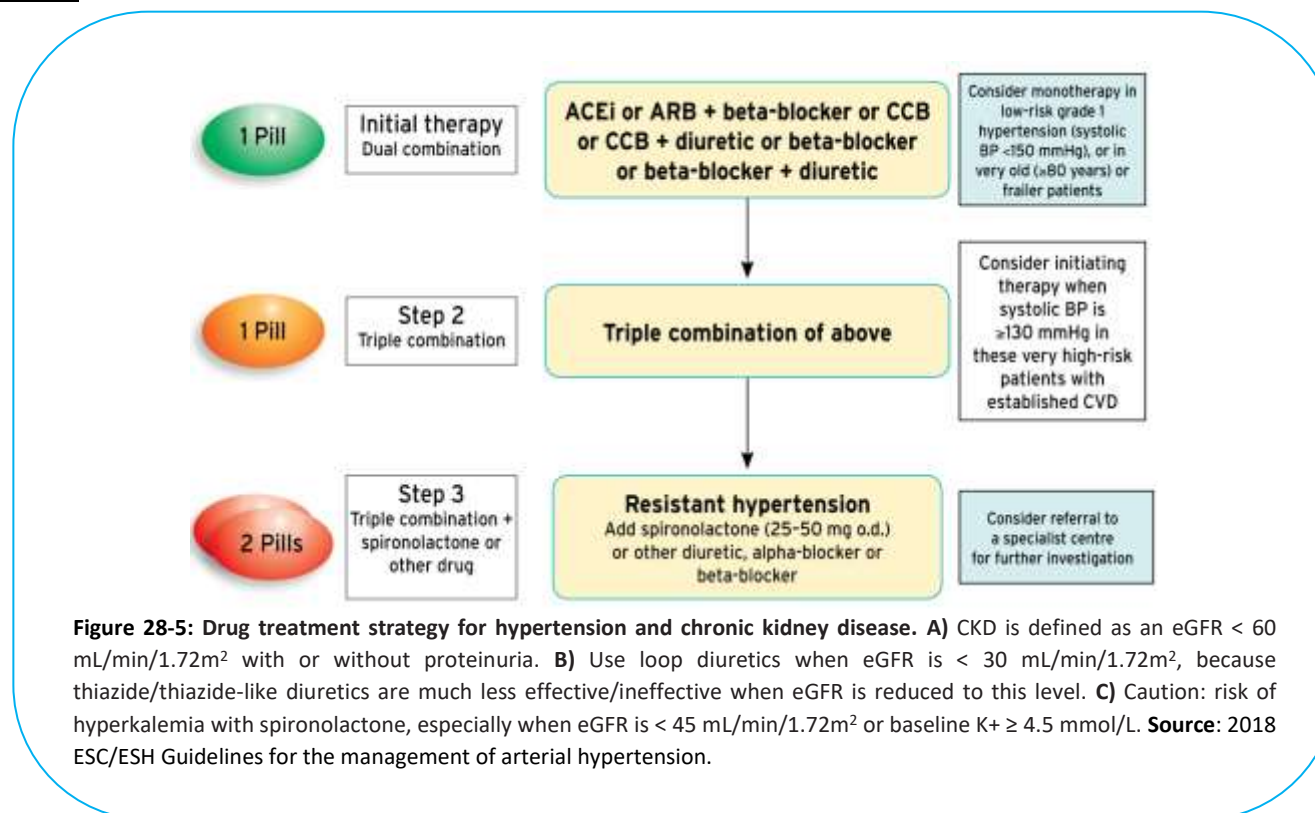


Table 28-25: ESC recommendations for therapeutic strategies for treatment of hypertension in chronic kidney disease:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.</i> | I | A |
| | | |

| | | |
|---|-----|---|
| <i>In patients with diabetic or non-diabetic CKD:</i> - It is recommended to lower SBP to a range of 130-139 mmHg. - Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes. | I | A |
| | IIa | C |
| RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria. | I | A |
| A combination of a RAS blocker with a CCB or a diuretic is recommended as initial therapy. | I | A |
| A combination of two RAS blockers is not recommended. | III | A |

▪ **Hypertension in CAD:**

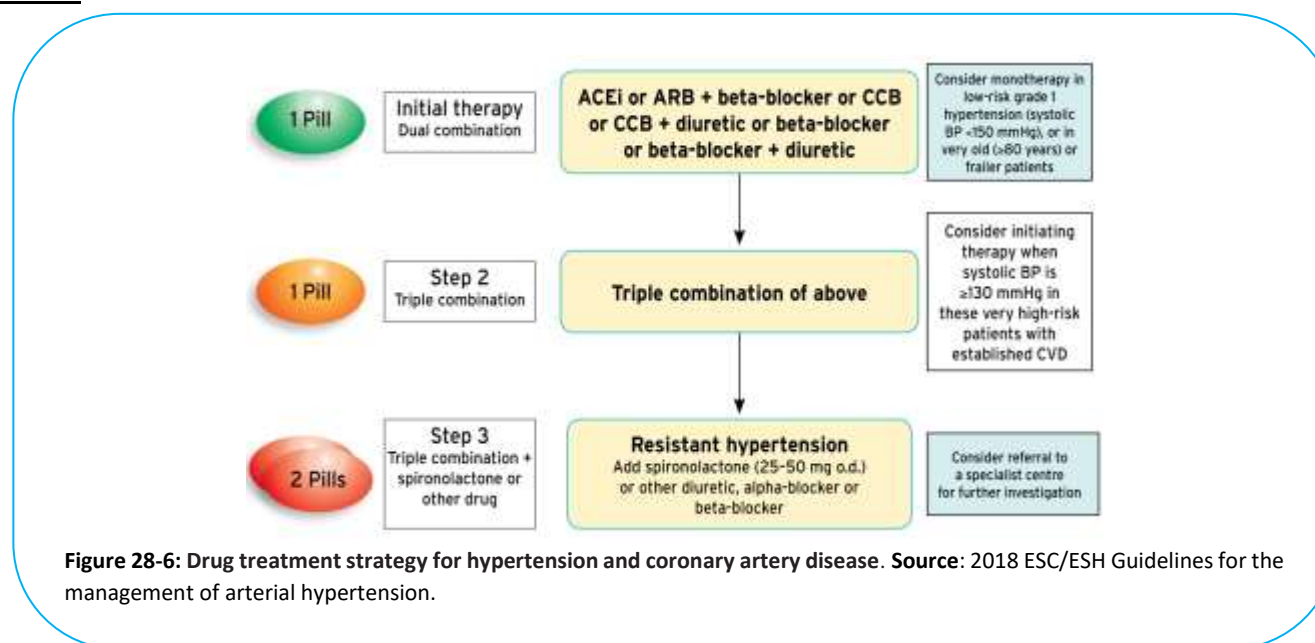


Table 28-26: ESC recommendations for Therapeutic strategies in hypertensive patients with coronary artery disease:

| Recommendations | Class | Level |
|--|--------------|--------------|
| In patients with CAD receiving BP-lowering drugs, it is recommended: | | |
| - To target SBP to ≤ 130 mmHg if tolerated, but not < 120 mmHg. | I | A |
| - In older patients (aged ≥ 65 years), to target to an SBP range of 130-140 mmHg. | I | A |
| - To target DBP to < 80 mmHg, but not < 70 mmHg. | I | C |
| In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment. | I | A |
| In patients with symptomatic angina, beta blockers and/or CCBs are recommended. | I | A |

▪ **Hypertensive patients with heart failure or LVH:**

| Table 28-27: ESC recommendations for therapeutic strategies in hypertensive patients with HF or LVH: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is $\geq 140/90$ mmHg. | IIa | B |
| In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required. | I | A |
| Dihydropyridine CCBs may be added if BP control is not achieved. | IIb | C |
| In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF. | IIa | B |
| Because no specific drug has proven its superiority, all major agents can be used. | I | C |
| In all patients with LVH: | | |
| • It is recommended to treat with an RAS blocker in combination with a CCB or diuretic. | I | A |

- SBP should be lowered to a range of 120-130 mmHg.

IIa

B

▪ **Hypertension patients with acute stroke and cerebrovascular disease:**

Table 28-28: ESC recommendations for therapeutic strategies in hypertensive patients with stroke and cerebrovascular stroke:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with acute intracerebral hemorrhage:</i> | | |
| - Immediate BP lowering is not recommended for patients with SBP < 220 mmHg. | III | A |
| - In patients with SBP ≥ 220 mmHg, careful acute BP lowering with i.v. therapy to < 180 mmHg should be considered. | IIa | B |
| <i>In acute ischemic stroke, routine BP lowering with antihypertensive therapy is not recommended, with the exceptions:</i> | III | A |
| - In patients with acute ischemic stroke who are eligible for i.v. thrombolysis, BP should be carefully lowered and maintained at < 180/105 mmHg for at least the first 24 h after thrombolysis. | IIa | B |
| - In patients with markedly elevated BP who do not receive fibrinolysis, drug therapy may be considered, based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset. | IIb | C |
| <i>In hypertensive patients with an acute cerebrovascular event, antihypertensive treatment is recommended:</i> | | |
| - Immediately for TIA. | I | A |
| - After several days in ischaemic stroke. | | |
| <i>In all hypertensive patients with ischaemic stroke or TIA, an SBP target range of 120-130 mmHg should be considered.</i> | IIa | B |

The recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker plus a CCB or a thiazide like diuretic.

I

A

▪ **Hypertensive patients with AF:**

Table 28-29: ESC recommendations for Therapeutic strategies in hypertensive patients with AF:

| Recommendation | Class | Level |
|--|--------------|--------------|
| <i>In patients with AF, screening for hypertension is recommended.</i> | I | C |
| <i>A beta-blocker or non-dihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed.</i> | IIa | B |
| <i>Stroke prevention with oral anticoagulation is recommended in patients with AF and hypertension, and a CHA₂DS₂-VASc score of ≥ 2 in men and ≥ 3 in women.</i> | I | A |
| <i>Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA₂DS₂-VASc score of 1).</i> | IIa | B |
| <i>Oral anticoagulants should be used with caution in patients with marked BP elevation (SBP ≥ 180 mmHg and/or DBP ≥ 100 mmHg); the aim should be to lower SBP to at least < 140 mmHg, and SBP lowering to < 130 should be considered. If this is not possible, then patients should make an informed decision that they accept that the stroke protection provided by the anticoagulant will be associated with higher bleeding risk.</i> | IIa | B |

▪ **Hypertensive patients with lower extremity arterial disease (LEAD):**

Table 28-30: ESC recommendations for Therapeutic strategies in hypertensive patients with LEAD:

| Recommendations | Class | Level |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|--|------------|----------|
| <i>BP-lowering treatment is recommended to reduce CV risk.</i> | I | A |
| <i>A combination of a RAS blocker, CCB, or diuretic should be considered as initial therapy.</i> | IIa | B |
| <i>Beta-blockers may also be considered.</i> | IIb | C |

▪ **Perioperative management of hypertension:**

| Table 28-31: ESC recommendations for Perioperative management of hypertension: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>It is recommended that newly diagnosed hypertensive patients who are scheduled for elective surgery should be preoperatively screened for HMOD and CV risk.</i> | I | C |
| <i>It is recommended to avoid large perioperative BP fluctuations during the perioperative period.</i> | I | C |
| <i>Non-cardiac surgery may not be deferred in patients with grade 1 or 2 hypertension (SBP <180 mmHg; DBP < 110 mmHg).</i> | IIb | C |
| <i>Perioperative continuation of beta-blockers is recommended in hypertensive patients on chronic treatment with these drugs.</i> | I | B |
| <i>Abrupt discontinuation of beta-blockers or centrally acting agents (e.g. clonidine) is potentially harmful and is not recommended.</i> | III | B |
| <i>Transient preoperative discontinuation of RAS blockers should be considered in patients with hypertension undergoing non cardiac surgery.</i> | IIa | C |

Follow-up of hypertensive patients:

- After the initiation of antihypertensive drug therapy, it is important to review the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects.

- SPC therapy should reduce BP within 1-2 weeks and may continue to reduce BP over the next 2 months.
- Once the BP target is reached, a visit interval of a few months is reasonable, and evidence has been obtained that no difference exists in BP control between 3- and 6-month intervals.
- Depending on the local organization of health resources, many of the later visits may be performed by non-physician health workers such as nurses.
- For stable patients, HBPM and electronic communication with the physician may also provide an acceptable alternative to reduce the frequency of visits.
- It is advisable to assess risk factors and asymptomatic organ damage at least every 2 years.

Important trials in Hypertension:

| Table 28-32: Clinical trials of Hypertension: | |
|---|--|
| Trial (date) | Summary |
| ACEIs: | |
| ACCOMPLISH (2008) | <p>Aim: To evaluate the safety and efficacy of the combination of amlodipine/benazepril, compared with hydrochlorothiazide (HCTZ)/benazepril in reducing CV morbidity and mortality in high-risk patients with systolic hypertension.</p> <p>Study: 11,506 patients with hypertension who were at high risk for CV events were assigned to receive treatment with either benazepril plus amlodipine <u>or</u> benazepril plus hydrochlorothiazide. The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing CV events in patients with hypertension who were at high risk for such events.</p> |
| ALLHAT (2002) | <p>Aim: To comparing the effects of amlodipine, lisinopril, or doxazosin versus chlorthalidone in patients with hypertension.</p> <p>Study: 33,357 participants ≥ 55 years with hypertension and at least 1 other CHD risk factor were randomly assigned to receive chlorthalidone (12.5 to 25 mg/d); amlodipine (2.5 to 10 mg/d); or lisinopril (10 to 40 mg/d) for planned follow-up of approximately 4 to 8 years. Thiazide-type diuretics are superior to ACEIs and CCBs in preventing one or more major forms of CVD in high-risk patients with hypertension and in patients with hypertension and diabetes.</p> |
| ARBs: | |
| LIFE (2002) | <p>Aim: To assess if losartan is more effective than atenolol in reducing CV morbidity and death in patients with essential hypertension and LVH.</p> |

| | |
|------------------------|--|
| | <p>Study: 9193 participants aged 55-80 years with essential hypertension (sitting blood pressure 160-200/95-115 mmHg) and LVH ascertained by ECG were assigned to once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years. Losartan seems to confer benefits beyond reduction in blood pressure.</p> |
| VALUE (2003) | <p>Aim: To investigate whether lowering BP with valsartan would yield better CV outcomes than treatment with amlodipine.</p> <p>Study: 13,449 patients ≥ 50 years old with hypertension were either randomized to amlodipine-based antihypertensive therapy or to valsartan-based antihypertensive therapy. HCTZ and other medications were added as needed to achieve a target of $< 140/90$ mmHg. Patients were followed for 30 months. The achieved BP control exceeds values reported in most published large-scale trials. BP control was achieved in both groups, but BP was slightly lower in the amlodipine-based group.</p> |
| CCBs: | |
| ALLHAT (2002) | See before |
| VALUE (2003) | See before |
| Syst-Eur (1997) | <p>Aim: To test the hypothesis that antihypertensive treatment of elderly patients with isolated systolic hypertension results in a significant change in stroke morbidity and mortality.</p> <p>Study: 4695 patients (> 60 years) were initially started on masked placebo. At three run-in visits 1 month apart, their average sitting systolic blood pressure was 160-219 mmHg with a diastolic blood pressure lower than 95 mmHg. After stratification for centre, sex, and previous cardiovascular complications, 4695 patients were randomly assigned to nitrendipine 10-40 mg daily, with the possible addition of enalapril 5-20 mg daily and hydrochlorothiazide 12.5-25.0 mg daily, or matching placebos. Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of CV complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major CV endpoints.</p> |

| | |
|--------------------------|---|
| Alpha-blockers: | |
| ALLHAT (2002) | <i>Doxazosin , See before</i> |
| Thiazides: | |
| SHEP (1991) | <p>Aim: <i>To assess the ability of antihypertensive drug treatment to reduce the risk of stroke in isolated systolic hypertension.</i></p> <p>Study: <i>In 551 persons aged ≥ 60 years with isolated systolic hypertension were randomized (2365 to active treatment, 2371 to placebo). SBP ranged from 160 to 219 mmHg and DBP < 90 mmHg. Antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.</i></p> |
| ALLHAT (2002) | <i>Chlorthalidone, See before</i> |
| ACCOMPLISH (2008) | <i>Hydrochlorothiazide, See before</i> |
| Diet: | |
| DASH (1997) | <p>Aim: <i>To test the effects of dietary patterns on blood pressure</i></p> <p>Study: <i>459 adults with SBP < 160 mm Hg and DBP of 80 to 95 mm Hg. For three weeks, the subjects were fed a control diet that was low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States. They were then randomly assigned to receive for eight weeks the control diet, a diet rich in fruits and vegetables, or a “combination” diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels. A diet rich in fruits, vegetables, and low-fat dairy</i></p> |

| | |
|---|---|
| | <i>foods and with reduced saturated and total fat can substantially lower blood pressure. This diet offers an additional nutritional approach to preventing and treating hypertension.</i> |
| Timing of taking antihypertensive drugs: | |
| Hygia (2020) | <p>Aim: <i>to test whether bedtime in comparison to usual upon awakening hypertension therapy exerts better cv disease risk reduction.</i></p> <p>Study: <i>19 084 hypertensive patients were assigned to ingest the entire daily dose of ≥ 1 hypertension medications at bedtime <u>or</u> all of them upon awakening. At inclusion and at every scheduled clinic visit (at least annually) throughout follow-up, ambulatory blood pressure (ABP) monitoring was performed for 48 h. Routine ingestion by hypertensive patients of ≥ 1 prescribed BP-lowering medications at bedtime, as opposed to upon waking, results in improved ABP control (significantly enhanced decrease in asleep BP and increased sleep-time relative BP decline, i.e. BP dipping) and, most importantly, markedly diminished occurrence of major CVD events.</i></p> |
| TIME (2022) | <p>Aim: <i>To evaluate if taking BP medications in the evening compared with the morning would be preferential among hypertensive individuals.</i></p> <p>Study: <i>24 610 individuals aged ≥ 18 years with hypertension and taking at least one antihypertensive medication were randomly assigned to take all of their usual antihypertensive medications in either the morning or in the evening. The primary endpoint was composite of vascular death or hospitalisation for non-fatal MI or non-fatal stroke. Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes.</i></p> |
| Intensive Blood pressure control: | |
| SPRINT (2015) | <p>Aim: <i>To compare the benefit of treatment of systolic BP to a target of less than 120 mm Hg with treatment to a target of less than 140 mmHg.</i></p> <p>Study: <i>9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased CV risk, but without diabetes, were randomly assigned to a systolic blood-pressure target of < 120 mmHg (intensive treatment) or a target of < 140 mmHg (standard treatment). The primary composite outcome was MI, other ACs, stroke, HF, or death from</i></p> |

| | |
|--------------------------------|---|
| | <i>CV causes. Among patients at high risk for CV events but without diabetes, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal MACE and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.</i> |
| STEP (2021) | <p>Aim: <i>To to assess whether intensive treatment (SBP target, 110 to < 130 mmHg) would reduce CV risk to a greater extent than standard treatment (target, 130 to <150 mm Hg) in Chinese patients 60 to 80 years of age with hypertension.</i></p> <p>Study: <i>9624 chinese patients 60 to 80 years of age with hypertension to a systolic blood-pressure target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). The primary outcome was a composite of stroke, ACS, acute decompensated HF, coronary revascularization, AF, or death from CV causes. In older patients with hypertension, intensive treatment with a SBP target of 110 to less than 130 mm Hg resulted in a lower incidence of CV events than standard treatment with a target of 130 to less than 150 mmHg.</i></p> |
| Renal denervation: | |
| Symplicity HTN-2 (2010) | <p>Aim: <i>To compare a strategy of renal sympathetic denervation with standard therapy among patients with treatment-resistant hypertension.</i></p> <p>Study: <i>106 patients who had a baseline systolic blood pressure of 160 mmHg or more (≥ 150 mmHg for patients with type 2 DM), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.</i></p> |
| Symplicity HTN-3 (2014) | <p>Aim: <i>To assess the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension.</i></p> <p>Study: <i>535 patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. This blinded trial did not show a</i></p> |

| | |
|--|--|
| | <i>significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control.</i> |
|--|--|

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Chapter 29:

Dyslipidemia

Evidence has confirmed that the key initiating event in atherogenesis is the retention of LDL and other cholesterol-rich lipoproteins within the arterial wall. The causal role of LDL-C, and other apo-B-containing lipoproteins, in the development of ASCVD is demonstrated beyond any doubt by genetic, observational, and interventional studies.

Lipids and lipoproteins:

▪ Digestion and absorption of lipids:

- The first step begins in the mouth where the enzyme lingual lipase, along with a small amount of phospholipid as an emulsifier, initiates the process of digestion. As a result, the fats become tiny droplets and separate from the watery components.
- **In the stomach:** Gastric lipase starts to break down triglycerides into *diglycerides* and *fatty acids*.
- **In the duodenum:** As stomach contents enter the small intestine, the digestive system sets out to manage a small hurdle, How to combine the separated fats (hydrophobic) with its watery fluids? The solution to this hurdle is **bile**. Bile attracts and holds onto fat while it is simultaneously attracted to and held on to by water, in a process called “**Emulsification**” which increases the surface area of lipids, making them more accessible to the digestive enzymes. Once the stomach contents have been emulsified, fat-breaking enzymes (pancreatic lipase) enters the small intestine, and breaks down the fats into free *fatty acids* and *monoglycerides*.
- Yet again, How will the fats pass through the watery layer of mucus that coats the absorptive lining of the digestive tract? As before, the answer is **bile**. Bile salts envelop the fatty acids and monoglycerides to form **micelles**. Micelles have a fatty acid core with a water-soluble exterior. This allows efficient transportation to the intestinal microvillus where, the fat components are released and disseminated into the cells.

○ Inside the intestinal cells, the monoglycerides and fatty acids reassemble themselves into triglycerides (TGs). TGs are combined with cholesterol and a protein carrier (ApoB 48) to produce TG-rich **lipoproteins** “known as **chylomicrons**”. Chylomicron is a large lipoprotein that enters the lymphatic system and will be released into the bloodstream via the jugular vein in the neck. Chylomicrons transport food fats perfectly through the body’s water-based environment to specific destinations such as the liver and other tissues.

▪ **Biological role of lipoproteins:**

○ **Structure:** Lipoproteins consist of:

- Inner core of lipid (esterified and unesterified cholesterol, triglycerides, and phospholipids) and
- Protein components (named Apolipoproteins) that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors.

○ **Function:** Lipoproteins transport lipids in plasma to tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation.

○ **Types of Lipoproteins:** There are six major lipoproteins in blood:

1. **Chylomicrons:** large lipoprotein that transports triglycerides and cholesterol esters from the digestive system into the bloodstream through the lymphatic system. Chylomicrons gradually release their triglycerides until all that is left of their composition is cholesterol-rich remnants. These remnants are used by the liver to formulate specific lipoproteins.
2. **Very low-density lipoproteins (VLDLs):** VLDLs are made in the liver when the remnants of chylomicrons are packaged together with triglycerides into lipoproteins containing apolipoprotein B (ApoB), then transport triglycerides from the liver to various tissues in the body. As the VLDLs travel through the circulatory system, the lipoprotein lipase strips the VLDL of triglycerides. As triglyceride removal persists, the VLDLs become intermediate-density lipoproteins (IDLs).
3. **Intermediate-density lipoproteins (IDLs):** IDLs transport a variety of cholesterol and little triglyceride. While travelling in the bloodstream, cholesterol is gained from other lipoproteins while circulating enzymes strip its phospholipid component. When IDLs return to the liver, they are transformed into low-density lipoprotein.

4. **Low-density lipoproteins (LDLs):** LDLs carry cholesterol and other lipids from the liver to tissue throughout the body. Some LDL is taken up by peripheral cells as a source of cholesterol. However, Most of the LDL particles are taken up by the hepatocytes through receptor systems specifically designed to bind with LDLs. Once inside the cell, the LDL is taken apart and its cholesterol is released then secreted in the bile.

In liver cells, these receptor systems aid in controlling blood cholesterol levels as they bind the LDLs. A deficiency of these LDL binding mechanisms will leave a high quantity of cholesterol traveling in the bloodstream, which can lead to heart disease or atherosclerosis.

5. **Lipoprotein(a):** Lp(a) assembly occurs on the hepatocyte surface. Its core composition resembles LDL surrounded by an outer membrane of phospholipids and free cholesterol. Its protein moiety comprises apolipoprotein B-100 (apoB) bound to apolipoprotein(a) (apo[a]). Lp(a) synthesis is primarily determined through the LPA gene. Lp(a) promotes ASCVD and calcific aortic valve stenosis via 4 mechanisms: vascular inflammation, atherogenesis, calcification, and thrombosis. European Atherosclerosis Society noted that Lp(a) levels of ≥ 50 mg/dL confer increased CV risk.
6. **High-density lipoproteins (HDLs):** HDLs have a very large protein composition (Apolipoprotein A1) coupled with low cholesterol content (20-30%) compared to the other lipoproteins. HDL particles scavenges “bad” cholesterol from the endothelium and lipid-laden macrophages (cholesterol efflux), then transport excess cholesterol back to the liver in a process called “**reverse cholesterol transport**”. The HDL particles can either transport cholesterol directly back to the liver, or interact with cholesterol ester transfer protein (CETP) to exchange cholesterol for TGs with TG-rich ApoB-containing lipoproteins (e.g VLDLs). The transferred cholesterol can then be taken back to the liver carried either by VLDL or LDL particles.

| Table 29-1: Characteristics of human plasma lipoproteins: | | | |
|---|---------------|-------------|-----------------|
| | Triglycerides | Cholesterol | Apolipoproteins |
| Chylomicrons | 90-95% | 1% | ApoB-48 |
| VLDL | 50-65% | 4-7% | ApoB-100 |
| IDL | 25-40% | 7-11% | ApoB-100 |
| LDL | 4-6% | 6-15% | ApoB-100 |

| | | | |
|---|------|------|--------|
| Lp(a) | 4-8% | 6-9% | Apo(a) |
| HDL | 75 | 5% | ApoA-1 |
| Chylomicrons are the largest lipoprotein in diameter (diameter related to amount of lipid content). However, HDL is the highest density lipoprotein (Density is related to the protein content) | | | |

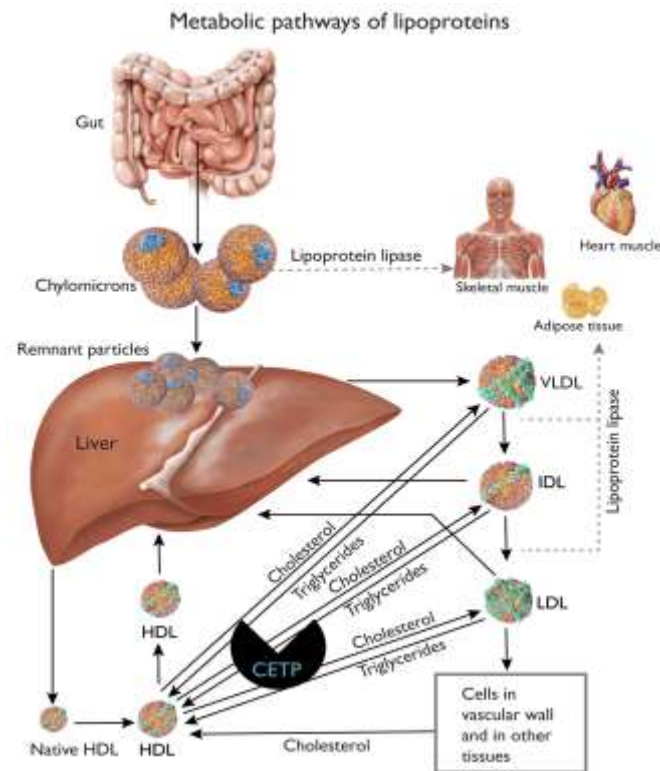


Figure 29-1: Lipoprotein transport and metabolism. Source: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Supplementary data

- **Effects of lipids and lipoproteins on the risk of atherosclerotic CV disease:**

Apo B is the protein found in all atherogenic particles, such as LDL, VLDL, and Lp(a). All ApoB-containing lipoproteins < 70 nm in diameter can cross the endothelial barrier, especially in the presence of endothelial dysfunction. ApoB-containing lipoproteins retained in the arterial wall provoke a complex process that leads to lipid deposition and the initiation of an

atheroma. Apo B levels correlate with the number of LDL particles and may predict CV outcomes better than LDL, especially in patients with low LDL levels who continue to have recurrent CV events.

- **LDL-C:** All the evidence showed that LDL-C particles have both a causal and cumulative effect on the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportionally to the absolute reduction in LDL-C.
- **HDL:** A spontaneously high HDL is protective against CAD as it indicates that “bad” cholesterol has been scavenged and will be eliminated through the CETP enzyme. Drugs that increase HDL by inhibiting CETP may saturate HDL and inhibit its capacity to scavenge cholesterol (dysfunctional HDL). This may paradoxically increase CV events. In fact, a pharmacological increase in HDL may not improve outcomes. However, Niacin increases HDL but also the efficacy of the scavenging effect by reducing VLDL, and reduces atherogenic lipoproteins, which explains the possible improvement of outcomes with niacin.
- **Triglycerides:** Triglycerides are associated with some increase in the risk of CV events, through their association with a high level of atherogenic lipoproteins (VLDL and VLDL remnants which are small enough to penetrate the endothelium), rather than a direct TG effect. Also, high VLDL precludes cholesterol elimination from HDL, which affects the efficacy of HDL scavenging. Thus, a high TG level reflects a high level of atherogenic lipoproteins, and mandates calculation and reduction of non-HDL cholesterol rather than TG itself.
- **Lipoprotein(a):** Lp(a) is < 70 nm in diameter and can freely flux across the endothelial barrier, where it can become -similarly to LDL- retained within the arterial wall and thus may increase the risk of ASCVD. Pro-atherogenic effects of Lp(a) have also been attributed to pro-coagulant effects as Lp(a) has a similar structure to plasminogen, and it has pro-inflammatory effects most likely related to the oxidized phospholipid load carried by Lp(a). Higher plasma Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a much weaker risk factor for most people than LDL-C.

Laboratory measurement of lipids and lipoproteins:

Quantification of lipids can be performed on whole plasma and quantification of lipoproteins can be achieved by measuring their protein component. Operationally, lipoproteins are classified based on their density.

- Plasma LDL-C can be measured directly using enzymatic techniques or preparative ultracentrifugation, but in clinical medicine it is most often calculated using the Friedewald formula:

$$\text{LDL-C (in mg/dL)} = \text{TC} - \text{HDL-C} - (\text{TG}/5)$$

When TG > 400 mg/dL (> 4.5 mmol/L), the formula cannot be used, especially in non-fasting samples.

For the general population, calculated LDL-C and direct LDL-C show very strong correlations. However, calculated LDL-C has been found to underestimate LDL-C when TG is ≥ 177 mg/dL.

- As an alternative to calculated LDL-C, non-HDL-C can be calculated as TC - HDL-C. It is a measure of the TC carried by all atherogenic ApoB-containing lipoproteins, including TG-rich particles in VLDL and their remnants. The targeting of non-HDL is particularly relevant in patients with high TGs (and thus high VLDL), whose atherogenic particles and risk may not be fully represented by LDL.

- **Fasting or non-fasting?**

Traditionally, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples have suggested that the difference is small for most lipid parameters. In most studies, non-fasting samples display a higher TG level of 27 mg/dL (0.3 mmol/L). For most individuals, this increment will be of no clinical significance.

- Because all ApoB-containing lipoproteins -including VLDL, TG-rich remnant particles, and LDL- contain a single ApoB molecule, quantitation of ApoB directly estimates the number of atherogenic particles in plasma. Automated, accurate, and inexpensive methods to measure ApoB are available. Fasting is not required because even in the post-prandial state, ApoB48-containing chylomicrons typically represent < 1% of the total concentration of circulating ApoB-containing lipoproteins.

Risk Stratification and Treatment targets:

The following scheme may be proposed:

- Evaluate the total CV risk of the individual using either the European SCORE or the American ASCVD Risk Estimator.
- Determine the treatment goals (depending on current risk).

- Involve the patient in decisions on CV risk management.
- Advice about the Lifestyle modifications to improve the lipid profile.
- Choose a statin regimen and, when necessary, additional treatments (e.g. ezetimibe or PCSK9 inhibitors) that can meet the treatment goals (percent and absolute value).
- If treatment goals are not achieved, uptitration of the statin dose may be required before additional LDL-lowering treatments are started.

| Table 29-2: ESC Recommendations for lipid analysis for CV disease risk estimation: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>TC is to be used for the estimation of total CV risk by means of the SCORE system.</i> | I | C |
| <i>HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.</i> | I | C |
| <i>LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.</i> | I | C |
| <i>TG analysis is recommended as part of the routine lipid analysis process.</i> | I | C |
| <i>Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.</i> | I | C |
| <i>ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.</i> | I | C |
| <i>Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels > 180 mg/dL who may have a lifetime</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolemia.</i> | | |
| <i>Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.</i> | Ila | C |

Table 29-3: ESC recommendations for Intervention strategies as a function of total cardiovascular risk and untreated LDL-C levels:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Primary Prevention: | | |
| Low risk (Total CV risk < 1%): | | |
| - < 116 mg/dl : <i>Lifestyle advice</i> | I | C |
| - 116:190 mg/dl : <i>Lifestyle intervention, consider adding drug if uncontrolled</i> | Ila | A |
| - > 190 mg/dl : <i>Lifestyle intervention and concomitant drug intervention</i> | Ila | A |
| Moderate risk (Total CV risk 1-5%): | | |
| - < 70 mg/dl : <i>Lifestyle advice</i> | I | C |
| - 70: 100 mg/dl : <i>Lifestyle advice</i> | Ila | A |
| - 100: 190 mg/dl : <i>Lifestyle intervention, consider adding drug if uncontrolled</i> | Ila | A |
| - > 190 mg/dl : <i>Lifestyle intervention and concomitant drug intervention</i> | Ila | A |
| High risk (Total CV risk 5-10%): | | |
| - < 70 mg/dl : <i>Lifestyle advice</i> | Ila | A |
| - 70: 100 mg/dl : <i>Lifestyle intervention, consider adding drug if uncontrolled</i> | Ila | A |
| - > 100 mg/dl : <i>Lifestyle intervention and concomitant drug intervention</i> | I | A |
| Very high risk (Total CV risk > 10%): | | |

| | | |
|--|-----|---|
| - < 55 mg/dl: <i>Lifestyle advice</i> | Ila | B |
| - 55:70 mg/dl: <i>Lifestyle intervention, consider adding drug if uncontrolled</i> | Ila | A |
| - > 70 mg/dl: <i>Lifestyle intervention and concomitant drug intervention</i> | I | A |
| Secondary Prevention (Very high risk): | | |
| - < 55 mg/dl: <i>Lifestyle intervention, consider adding drug if uncontrolled</i> | Ila | A |
| - > 55 mg/dl: <i>Lifestyle intervention and concomitant drug intervention</i> | I | A |

Table 29-4: Treatment targets and goals for cardiovascular disease prevention:

| | |
|-------------------|---|
| Smoking | <i>No exposure to tobacco in any form.</i> |
| Diet | <i>Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit, and fish.</i> |
| Physical activity | <i>3.5-7 h moderately vigorous physical activity per week or 30-60 min most days.</i> |
| Body weight | <i>BMI 20-25 kg/m², and waist circumference < 94 cm (men) and < 80 cm (women).</i> |
| Blood pressure | <i>< 140/90 mmHg ⁽¹⁾</i> |
| Diabetes | <i>HbA1c: < 7% (< 53 mmol/mol).</i> |

(1) Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.

| | |
|-----------------------------|---|
| LDL-C ⁽¹⁾ | <ul style="list-style-type: none"> ○ Very-high risk in primary or secondary prevention: A therapeutic regimen that achieves $\geq 50\%$ LDL-C reduction from baseline ⁽²⁾ and LDL-C goal of < 55 mg/dL (< 1.4 mmol/L). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. ○ High risk: A therapeutic regimen that achieves $\geq 50\%$ LDL-C reduction from baseline and an LDL-C goal of < 70 mg/dL (< 1.8 mmol/L). ○ Moderate risk: A therapeutic regimen that achieves LDL < 100 mg/dL (< 2.6 mmol/L). ○ Low risk: A therapeutic regimen that achieves LDL < 116 mg/dL (< 3.0 mmol/L). |
| Non-HDL-C | Non-HDL-C secondary goals are < 85 , 100 , and 130 mg/dL for very-high-, high-, and moderate-risk people, respectively (Goals are 30 mg/dL higher than the corresponding LDL goal) |
| ApoB | ApoB secondary goals are < 65 , 80 , and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively. |
| Triglycerides | No goal, but < 150 mg/dL (< 1.7 mmol/L) indicates lower risk and higher levels indicate a need to look for other risk factors. |

(1) The LDL level in neonates is only ~ 40 mg/dl, and it appears that human cells only require an LDL plasma level of 25 mg/dl. Wild mammalian species have LDL ~ 40 mg/dl and rarely develop atherosclerosis (monkey, horse, elephant). Human hunter-gatherer societies, which carry on the Paleolithic lifestyle, and rural Chinese have LDL cholesterol in that range as well and show no evidence of atherosclerosis, even late in life. The same applies to many patients with genetic loss-of-function of PCSK9. All this led to the suggestion that LDL is at the center of atherosclerosis and a very low LDL may prevent the initiation of atherosclerosis. This also suggests that a very low LDL is safe. Meta-analysis of clinical trials has indicated that the relative reduction in CVD risk is proportional to the absolute reduction of LDL-C, irrespective of the drug(s) used to achieve such change, with no evidence of a lower limit for LDL-C values or 'J-curve' effect. Data from PCSK9 trials concur that a very low LDL, even < 25 mg/dl, is safe (ODYSSEY long-term trial). A very low LDL level, however, may not fully prevent the progression of a pre-existing atherosclerosis.

(2) The term 'baseline' refers to the LDL-C level in a person not taking any lipid-lowering medication, or to the extrapolated baseline value for those who are on current treatment.

Table 29-5: ESC Recommendations for treatment goals for LDL-C:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In secondary prevention for patients at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 55 mg/dL (< 1.4 mmol/L) are recommended.</i> | I | A |
| <i>In primary prevention for individuals at very-high risk but without FH, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 55 mg/dL (< 1.4 mmol/L) are recommended.</i> | I | C |
| <i>In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 55 mg/dL (< 1.4 mmol/L) should be considered.</i> | IIa | C |
| <i>For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of < 40 mg/dL (< 1.0 mmol/L) may be considered.</i> | IIb | B |
| <i>In patients at high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 70 mg/dL (< 1.8 mmol/L) are recommended.</i> | I | A |
| <i>In individuals at moderate risk, LDL-C goal of < 100 mg/dL (< 2.6 mmol/L) should be considered.</i> | IIa | A |
| <i>In individuals at low risk, an LDL-C goal < 116 mg/dL (< 3.0 mmol/L) may be considered.</i> | IIb | A |

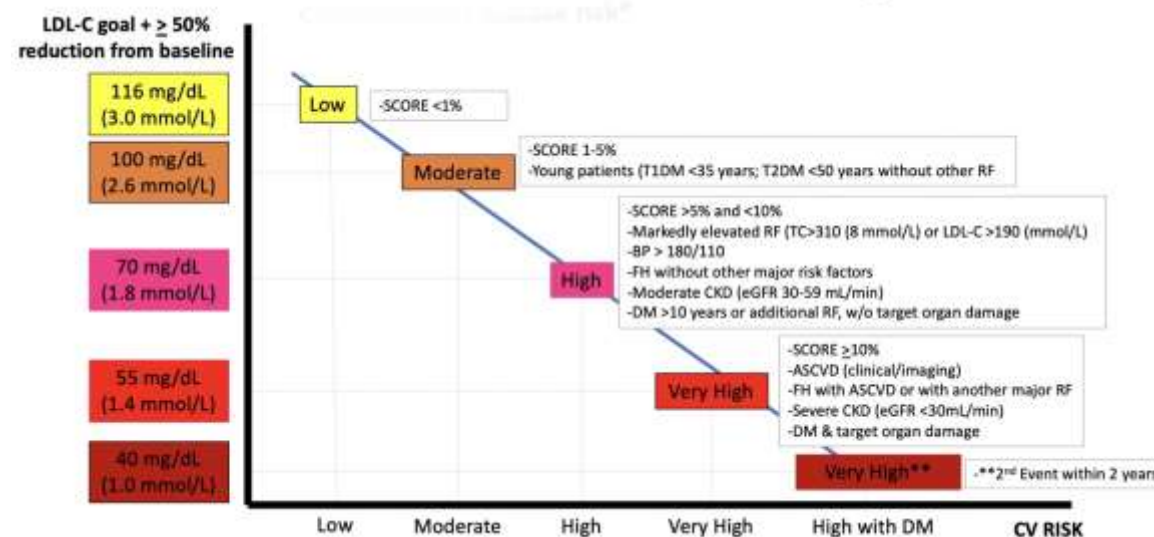


Figure 29-2: Treatment goals for LDL-C across categories of total CV disease risk. Source: 2019 ESC/EAS Guidelines for the management of dyslipidemias.

Lifestyle modifications to improve the lipid profile:

▪ **Body weight and physical activity:**

Since overweight, obesity, and -in particular- abdominal adiposity often contribute to dyslipidemia, caloric intake should be reduced and energy expenditure increased in those with excessive weight and/or abdominal adiposity.

▪ **Dietary supplements for the treatment of dyslipidemias:**

Nutritional evaluation of functional foods includes not only the search for clinical evidence of beneficial effects relevant to improved health or the reduction of disease risk, but also the demonstration of good tolerability. Overall, the available evidence

on functional foods so far identified in this field is incomplete; the major gap is an absence of diet-based intervention trials of enough duration to be relevant for the natural history of dyslipidemia and CVD.

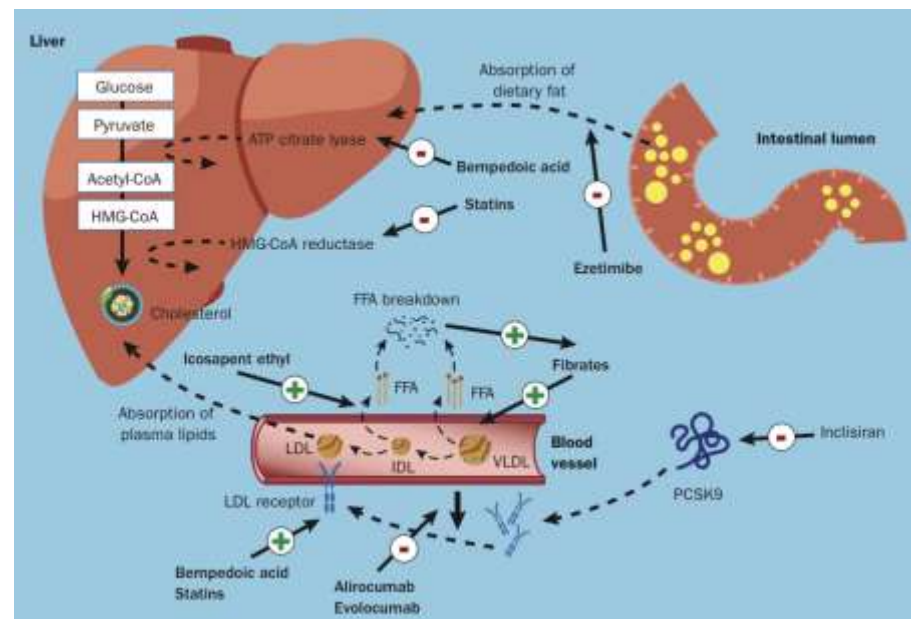
Table: 29-6: Impact of specific lifestyle changes on lipid levels:

| Lifestyle interventions | Effects to reduce TC and LDL-C | Effects to reduce TG-rich lipoprotein | Effects to increase HDL-C |
|--|--------------------------------|---------------------------------------|---------------------------|
| <i>Avoid dietary trans fats</i> | ++ | | ++ |
| <i>Reduce dietary saturated fats</i> | ++ | + | |
| <i>Increase dietary fibre</i> | ++ | | |
| <i>Use functional foods enriched with phytosterols</i> | ++ | | |
| <i>Use red yeast rice nutraceuticals</i> | ++ | | |
| <i>Reduce dietary cholesterol</i> | + | | |
| <i>Reduce total amount of dietary carbohydrates</i> | | +++ | ++ |
| <i>Reduce intake of mono- and disaccharides</i> | | ++ | |
| <i>Reduce excessive body weight</i> | + | + | ++ |
| <i>Increase habitual physical activity</i> | + | ++ | +++ |
| <i>Reduce alcohol intake</i> | | +++ | ++ |
| <i>Quit smoking</i> | | | + |
| <i>Use supplements of n-3 polyunsaturated fats</i> | | ++ | |

Pharmacological treatment of dyslipidaemias:

For more details, see chapter: Cardiovascular Pharmacology

The highest tolerable dose of a statin, in addition to lifestyle modifications, is the current standard of care for achieving LDL-C goals. However, a \approx 75-85% of statin-treated patients at high or very high CV risk fail to reach guideline-recommended LDL-C goals. As such, there is a need for additional, non-statin lipid-lowering therapies to reduce the residual risk of MACEs in those patients. Non-statin lipid-lowering therapies used as alternatives or adjuncts to statins include those that, like statins, lower plasma LDL-C levels by reducing the synthesis of cholesterol (e.g. bempedoic acid), while others work by decreasing the intestinal absorption of cholesterol (ezetimibe) or by increasing the hepatic clearance of cholesterol (bile acid sequestrants). Another strategy for lowering plasma LDL-C levels based on enhanced cholesterol clearance involves the targeting of proprotein convertase subtilisin/kexin type 9 (PCSK9) which has a central regulatory role in LDL receptor (LDLR) recycling within hepatocytes, which is the major route for LDL-C clearance from the circulation.



hepatocytes, which in turn results in increased uptake of LDL from the blood, and decreased plasma concentrations of LDL and other ApoB-containing lipoproteins, including TG-rich particles.

- **Effects on lipids:**

- **LDL-C:** The degree of LDL-C reduction is dose-dependent and varies between the different statins. A high intensity regimen is defined as the dose of a statin that, on average, reduces LDL-C by $\geq 50\%$; moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-50%.

Notably, there is considerable inter-individual variation in LDL-C reduction with the same dose of drug. Poor responses to statin treatment in clinical studies are to some extent caused by poor compliance, but may also be explained by genetic backgrounds.

- **Triglycerides:** Statins usually reduce TG levels by 10-20% from baseline values.
- **HDL-C:** In a meta-analysis, elevations in HDL-C levels varied with dose among the respective statins; such elevations ranged from 1-10%.
- **Lipoprotein(a):** Statins only marginally affect Lp(a) plasma levels.

N.B:

- **Rule of six:** Doubling the statin dose lowers LDL by 6% more, but is associated with a more significant increase in myopathy (e.g. increasing the atorvastatin to 80 mg from 10 mg reduces LDL by 60% vs. 40%).
- Statins are not effective in a few specific groups, notably those with HF or patients receiving hemodialysis.
- Although statins are generally very well tolerated, they do have some specific adverse effects on muscle, glucose hemostasis, and hemorrhagic stroke. Myopathy is the most clinically relevant adverse effect.

- **Bempedoic acid:**

- **Mechanism of action:** Bempedoic acid is a novel, first-in-class, oral small molecule that inhibits cholesterol synthesis by inhibiting the action of ATP citrate lyase, a cytosolic enzyme upstream of HMG-CoA reductase.

- **Effects on lipids:** Bempedoic acid monotherapy lowered LDL-C in patients not taking a statin by about 30%. Bempedoic acid + ezetimibe lowered LDL-C in patients not on statins by 50%. Bempedoic acid was associated with a lower risk of major adverse CV events (CLEAR trial).

- **Ezetimibe (Cholesterol absorption inhibitors):**

- **Mechanism of action:**

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol at the level of the brush border of the intestine [by interacting with the Niemann-Pick C1-like protein 1 (NPC1L1)] without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption, ezetimibe reduces the amount of cholesterol delivered to the liver. Therefore, the liver reacts by upregulating LDLR expression, which in turn leads to increased clearance of LDL from the blood.

- **Effects on lipids:**

Ezetimibe in monotherapy (10 mg/day) reduces LDL-C by 15-22%.

Ezetimibe added to ongoing statin therapy reduces LDL-C by an additional 21-27%.

RCTs support the use of ezetimibe as second-line therapy in association with statins when the therapeutic goal is not achieved, or in cases where a statin cannot be prescribed.

- **Bile acid sequestrants:**

- **Mechanism of action:**

Bile acids are synthesized in the liver from cholesterol and are released into the intestinal lumen, but most of the bile acid is returned to the liver from the terminal ileum via active absorption.

Bile acid sequestrants (cholestyramine, colestipol and colesevelam) are not systemically absorbed or altered by digestive enzymes, so they bind the bile acids and prevent the reabsorption of both the drug and cholesterol into the blood, and thereby remove a large portion of the bile acids from the enterohepatic circulation. The liver, depleted of bile, synthesizes more from

hepatic cholesterol, therefore increasing the hepatic demand for cholesterol and increasing LDLR expression, which results in a decrease of circulating LDL.

- **Effects on lipids:** Bile acid sequestrants reduced LDL-C by 18-25%. No major effect on HDL-C has been reported, while TGs may increase in some predisposed patients. Colesevelam can also reduce glucose levels in hyperglycaemic patients.

In clinical trials, bile acid sequestrants have contributed greatly to the demonstration of the efficacy of LDL-C lowering in reducing CV events in hypercholesterolaemic people, with a benefit proportional to the degree of LDL-C lowering. Of note, these studies were performed before many of the modern treatment options were available.

- **Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors:**

When PCSK9 protein binds to LDLR, it reduces LDLR expression by promoting LDLR lysosomal catabolism which results in a subsequent increase in plasma LDL concentrations. On the contrary, the lower concentration or function of PCSK9 is related to lower plasma LDL-C levels.

PCSK9 inhibitors include two types: **(1)** Monoclonal antibodies that reduce the plasma level of PCSK9. It includes Alirocumab and Evolocumab. **(2)** Small interfering RNA (siRNA) that prevents hepatic synthesis of PCSK9. Inclisiran is a first-in-class.

- (1) Anti-PCSK9 Monoclonal Antibodies:**

- **Mechanism of action:**

Alirocumab and Evolocumab are monoclonal antibodies that reduce the plasma level of PCSK9, which result in increased expression of LDLRs at the cell surface and therefore in a reduction of circulating LDL-C levels.

Statin treatment increases circulating PCSK9 serum levels, and thus the best effect of these drugs has been demonstrated in combination with statins.

- **Effects on lipids:**

In clinical trials, alirocumab and evolocumab -either alone or in combination with statins, and/or other lipid-lowering therapies- reduced LDL-C levels on average by 60%, depending on dose. They also lowered TG levels by 26%, and raised HDL-C and ApoA-I by 9 and 4%, respectively. In contrast to statins, PCSK9 inhibitors reduces Lp(a) plasma levels.

(2) Small interfering RNA (Inclisiran):

- **Mechanism of action:** Inclisiran is a long-acting, subcutaneously administered small interfering or 'silencing' RNA (siRNA)-based therapeutic oligonucleotide, specifically inhibits synthesis of PCSK9 in the liver, leading to increased hepatic uptake of circulating LDL-C and, hence, lowered plasma LDL-C levels.

The recommended dose is 300 mg administered as a single subcutaneous injection on day 1, day 90 and every 6 months thereafter.

- **Effects on lipids:** Inclisiran led to an LDL-C reduction of ~50% after 1.5 years of follow-up (meta-analysis of ORION-9, -10, and -11 trials). Although impressive, ~30% did not achieve an LDL-C < 70 mg/dl, highlighting the continued need for identifying additional lipid-lowering therapies.

- **Lomitapide:**

The microsomal TG transfer protein (MTP) transfers TGs and phospholipids from the endoplasmic reticulum to ApoB, as a necessary step in the formation of VLDL. Lomitapide is an MTP inhibitor thus prevents the formation of VLDL in the liver and of chylomicrons in the intestine.

Lomitapide is used as an oral treatment of HoFH. It should be noted that the drug's effect on CV outcomes has not yet been determined.

As a consequence of its mechanism of action, lomitapide has been shown to be associated with increased aminotransferase levels, which most likely reflects the increased fat in the liver, as well as poor GI tolerability.

- **Mipomersen:**

Mipomersen is an antisense oligonucleotide able to bind and degrade the messenger RNA (mRNA) of ApoB-100. An adjunct to lipid-lowering medications and diet, mipomersen is indicated to reduce LDL-C in patients with HoFH.

Mipomersen is currently approved by the US Food and Drug Administration (FDA), but not by the European Medicines Agency (EMA).

Reactions at the injection site are the most common adverse effects observed in patients treated with mipomersen. However, the main concerns regarding mipomersen's safety are related to liver toxicity.

- **Fibrates:**

- **Mechanism of action:**

Fibrates are agonists of peroxisome proliferator-activated receptor- α (PPAR- α), acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. As a consequence, fibrates have good efficacy in lowering fasting TG, post-prandial TGs levels and TG-rich lipoprotein (TRL) remnant particles.

In CV outcome trials, the risk reduction appeared to be proportional to the degree of non-HDL-C lowering.

- **Effects on lipids:** Fibrates are the most effective agents in lowering TGs. Clinical impacts on lipid profiles vary among members of the fibrate class, but are estimated to reach a 50% reduction of the TG level, a $\leq 20\%$ reduction of the LDL-C level (but a paradoxical LDL-C increase may be observed with high TG levels by converting some VLDL into LDL), and an increase of the HDL-C level of $\leq 20\%$.

- **n-3 fatty acids:**

- **Mechanism of action:**

The n-3 (or omega-3) fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] can be used at pharmacological doses to lower TGs. n-3 fatty acids (2-4 g/day) affect serum lipids and lipoproteins, in particular VLDL concentrations. The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to decreased secretion of ApoB.

- **Effects on lipids:** n-3 fatty acids reduce TGs, but their effects on other lipoproteins are trivial.

A meta-analysis, including 79 trials, reported no overall effect of omega-3 PUFAs on total mortality with only a suggestion that omega-3 fatty acids reduced CHD events. A recent secondary prevention trial, REDUCE-IT, showed that EPA 4 grams daily significantly reduced CV events.

- **Nicotinic acid:**

Nicotinic acid has key action sites in both the liver and adipose tissue.

- In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 resulting in decreased secretion of VLDL particles, which is also reflected in reductions of plasma levels of both IDL and LDL particles. Nicotinic acid primarily raises HDL-C and ApoA1 by stimulating ApoA1 production in the liver.
- In the adipose tissue, Niacin reduces fat degradation which reduces the release of free fatty acids in the circulation, reducing VLDL synthesis.

No medication containing nicotinic acid is currently approved in Europe.

▪ **Cholesterol ester transfer protein (CETP) inhibitors:**

CETP inhibitors have led to the greatest elevations in HDL-C levels $\geq 100\%$ on a dose-dependent basis.

CETP inhibitors include: Torcetrapib (studied in ILLUMINATE trial, stopped due to increased mortality), Dalcetrapib (failed to show any benefit in ACS patients in the dal-OUTCOMES trial) and Evacetrapib (studied in the ACCELERATE trial, terminated due to futility).

Recently, Anacetrapib, which raises HDL-C and ApoA-I levels (by 104% and 36%, respectively), and lowers LDL-C and ApoB (by 17% and 18%, respectively), was studied in the REVEAL trial. It reduced major coronary events by 9% over a median of 4.1 years. This drug has not been submitted for regulatory approval.

| Table 29-7: ESC Recommendations for pharmacological treatment of dyslipidemia: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| For LDL-C lowering: | | |
| <i>It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.</i> | I | A |
| <i>If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.</i> | I | B |

| | | |
|---|------------|----------|
| <i>For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.</i> | IIb | C |
| <i>For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.</i> | I | A |
| <i>For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.</i> | I | C |
| <i>If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.</i> | IIa | C |
| <i>If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.</i> | IIb | C |
| <i>If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.</i> | IIb | C |
| Management of hypertriglyceridemia: | | |
| <i>Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridemia [triglycerides > 200 mg/dL (> 2.3 mmol/L)].</i> | I | A |
| <i>In high-risk (or above) patients with triglycerides > 135 mg/dL (> 1.5 mmol/L) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2x2 g/day) may be considered in combination with a statin.</i> | IIb | B |
| <i>In patients taking statins who are at LDL-C goal with triglycerides > 200 mg/dL (> 2.3 mmol/L), fenofibrate or bezafibrate may be considered.</i> | IIb | B |

In high-risk patients who are at LDL-C goal with TG levels > 200 mg/dL (> 2.3 mmol/L), fenofibrate or bezafibrate may be considered in combination with statins.

IIb

C

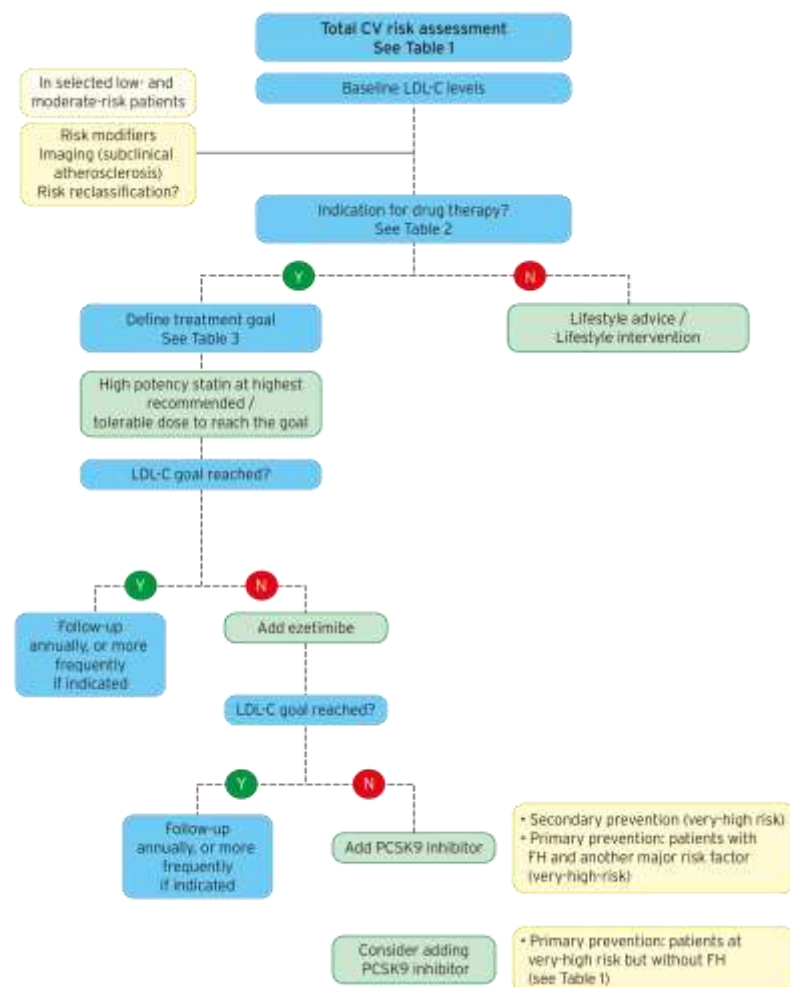


Figure 29-4: Treatment algorithm for pharmacological LDL-C lowering. Source: 2019 ESC/EAS Guidelines for the management of dyslipidemias.

▪ **Clinical Benefits of lowering LDL-C:**

- The expected clinical benefits of treatment to lower LDL-C for any person can be estimated; it depends on the intensity of therapy, the baseline LDL-C level, the expected absolute reduction in LDL-C, and the baseline estimated risk of atherosclerotic cardiovascular disease. The intensity of therapy should be selected to achieve the recommended proportional reduction in LDL-C based on the person's estimated risk of atherosclerotic CV disease. Multiplying the proportional reduction in LDL-C by a person's baseline LDL-C level estimates the expected absolute reduction in LDL-C that is likely to be achieved with that drug.
- The Cholesterol Treatment Trialists' (CTT) meta-analysis of 26 RCTs show that each decrease in LDL-C of 40 mg/dL (1.0 mmol/L) leads to a ~22% relative risk reduction in major vascular events and total mortality by 10% over 5 years. Therefore, larger absolute reductions in LDL-C lead to larger proportional reductions in risk.

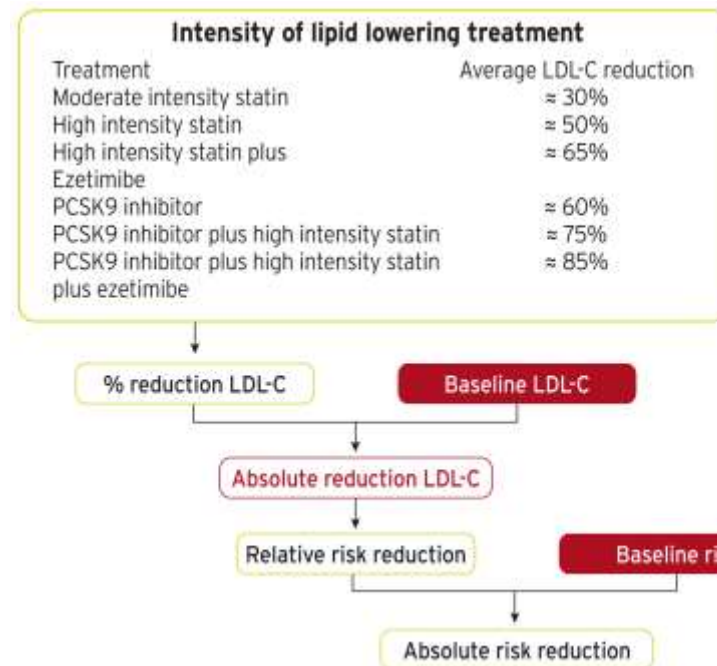


Figure 29-5: Expected clinical benefits of LDL-C-lowering therapies. Source:2019 ESC/EAS Guidelines for the management of dyslipidaemias.

Familial dyslipidemias

Table 29-8: Fredrickson classification of hyperlipidemias (Genetic Dyslipidemias)

| Type | Synonyms | Defect | Increased lipoprotein | Main symptom | Treatment |
|-----------------|--|--|-----------------------|--|---|
| Type I | Familial hyperchylomicronemia (Buerger-Gruetz syndrome) | -Lipoprotein lipase (LPL) deficiency -ApoCII deficiency | Chylomicron | Acute pancreatitis Lipemia retinalis, eruptive skin xanthomas, hepatosplenomegaly | Diet control |
| Type IIa | Familial hypercholesterolemia | LDL receptors deficiency (Autosomal dominant) | LDL | Xanthelasma, Arcus senilis, tendon xanthoma, early CV diseases (if not treated) | Bile acid sequestrants, statins, niacin |
| Type IIb | Familial combined hyperlipidemia | Decreased LDL receptor and increased ApoB | LDL and VLDL | | Statins, niacin, fibrates |
| Type III | Remnant hyperlipidemia <u>or</u> Familial dyslipoproteinemia | Defect in ApoE2 synthesis | Mixed hyperlipidemia | Tuboeruptive xanthomas | Fibrates (1 st line) |

| | | | | | |
|---|-------------------------------|---|-----------------------------|---|---------------------------|
| | | (Autosomal recessive) | a (LDL-C and triglycerides) | Palmar xanthomas Yellow palmar creases Early onset 30 y, IHD, associated with PVD | |
| Type IV | Familial hypertriglyceridemia | Increased VLDL production and decreased elimination | VLDL | Eruptive xanthoma Can cause pancreatitis at high triglycerides levels. | Fibrates, niacin, statins |
| Type V | | Increased VLDL production and decreased LPL | VLDL and chylomicrons | | Fibrates, niacin |
| <ul style="list-style-type: none"> ○ High triglycerides are a component of each of these dyslipidemias except Type IIa (Familial hypercholesterolemia). ○ The two most common dyslipidemias are type IIb and Type IV. Together, these two forms accounts for 85% of familial dyslipidemias. | | | | | |

- **Familial lipoprotein lipase deficiency** (familial chylomicron syndrome): it is autosomal recessive that usually presents in childhood and characterized by very severe **hypertriglyceridemia** with episodes of abdominal pain, recurrent pancreatitis,

eruptive cutaneous xanthomata, and hepatosplenomegaly. Clearance of chylomicrons from the plasma is impaired, causing triglycerides to accumulate in plasma (causing milky lipemic appearance). Symptoms usually resolve with restriction of total dietary fat to ≤ 20 g/day. The lipid-lowering drugs that are used to treat other disorders of lipid metabolism are not effective in individuals with familial LPL deficiency. Recently, gene therapy for LPL deficiency has been developed and tested in clinical trials, and the **alipogene tiparvovec** was approved by the EMA in 2013.

- **Familial combined hyperlipidaemia (FCH):** is a highly prevalent mixed dyslipidaemia (1:100-200) characterized by elevated levels of LDL-C, TGs, or both, and is an important cause of premature CAD. FCH is not linked to a single genetic cause, but the phenotype is high LDL-C and/or high TGs. Therefore, the diagnosis is commonly missed in clinical practice; the combination of ApoB > 120 mg/dL and TGs > 133 mg/dL with a family history of premature CVD can be used to identify people who most probably have FCH.
- **Familial dysbetalipoproteinaemia** (i.e. type III hyperlipoproteinaemia; remnant removal disease): is rare autosomal recessive disorder with variable penetrance. The majority of cases are homozygous for the E2 isoform of **ApoE**. ApoE is important for the hepatic clearance of chylomicron remnants and IDL. Familial dysbetalipoproteinaemia produces a characteristic clinical syndrome in which both TC and TGs are elevated, both in the range of 7-10 mmol/L.

In severe cases, patients develop tuberoeruptive xanthomas, particularly over the elbows and knees, and palmar xanthomata in the skin creases of the hands and wrists.

The risk of CAD is very high, and accelerated atherosclerosis of the femoral and tibial arteries is prevalent. The syndrome is usually not expressed at young age or in women before menopause.

Most cases respond well to treatment with a statin or, if dominated by high TGs, a fibrate; often a combination of a statin and a fibrate may be needed.

- **Familial hypercholesterolaemia (FH):**

(A) Heterozygous familial hypercholesterolaemia (HeFH):

- FH is a common codominant monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C. It is caused by loss-of-function mutations in the **LDLR** or **apoB** genes, or a gain-of-function mutation in the **PCSK9** gene; around 95% of FH cases are caused by mutations in LDLR.
- If left untreated, men and women with HeFH typically develop early CAD before the ages of 55 and 60 years respectively.
- The diagnosis of FH is usually based on clinical presentation. The commonly used criteria for diagnosis is the Dutch Lipid Clinic Network criteria. The diagnosis can be verified by showing causative mutations in the pathogenic genes. However, the frequency of detectable mutations in patients with a clinically definite or probable HeFH is between 60-80% (suggests polygenic cause or unidentified other genes).
- Genetic testing and cascade screening: Probands (index cases) should be identified according to the following criteria:
 - TC \geq 310 mg/dL (\geq 8 mmol/L) without treatment in an adult or adult family member (or $>$ 95th percentile by age and gender for country).
 - Premature CHD in the patient or a family member.
 - Tendon xanthomas in the patient or a family member; or
 - Sudden premature cardiac death in a family member.

(B) Homozygous familial hypercholesterolaemia:

- HoFH is a rare and life-threatening disease. Most patients develop CAD and aortic stenosis before the age of 20 years and die before 30 years of age.
- **Clinical criteria:**
 - LDL-C criteria: Untreated LDL-C $>$ 400 mg/dL is suggestive of HoFH requiring further investigation to confirm the diagnosis.
 - Additional criteria: Cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with heterozygous FH in both parents
- **Genetic criteria:** Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the **LDLR**, **APOB**, **PCSK9**, or **LDLRAP1** genes or $>$ 2 such variants at different loci.

- **Management:** Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy. Within 8 weeks, PCSK9-directed therapy should be considered. Lipoprotein apheresis fortnightly or even weekly is used adjunctive to other lipid-lowering therapy. Liver transplantation may be considered a last resort, despite maximal therapy in a small subset of patients with HoFH.
- **Treatment goals:**
 - In adult patients with HoFH (≥ 18 years), the LDL-C goal is < 70 mg/dL, and < 55 mg/dL with additional ASCVD-risk factors (elevated Lp(a), DM) or established ASCVD.
 - In children and adolescents, an LDL-C goal of < 115 mg/dL is recommended.

(C) Familial hypercholesterolemia in children:

FH is diagnosed in children based on phenotypic criteria including elevated LDL-C plus a family history of elevated LDL-C, premature CAD, and/or positive genetic testing. Testing during childhood is optimal to discriminate between FH and non-FH using LDL-C. In children with a family history of high cholesterol or premature CHD, an accepted cut-off is ≥ 160 mg/dL. If a parent has a known genetic defect, the diagnostic level for the child is ≥ 130 mg/dL. A heart-healthy diet should be adopted early in life and statin treatment should be considered at 6-10 years of age. The goal in children > 10 years of age is LDL-C < 135 mg/dL and at younger ages a $\geq 50\%$ reduction of LDL-C.

| Table 29-9: Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia: | |
|--|----------|
| Criteria | Points |
| 1) Clinical history: | |
| <i>Patient with premature CAD (men aged < 55; women < 60 years)</i> | 2 |
| <i>Patient with premature cerebral or peripheral vascular disease (men aged < 55; women < 60 years)</i> | 1 |
| 2) Family history: | |
| <i>First-degree relative with known premature (men aged < 55 years; women < 60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile</i> | 1 |

| | |
|--|----------|
| <i>First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged < 18 years with LDL-C above the 95th percentile</i> | 2 |
| 3) Physical examination ⁽¹⁾: | |
| <i>Tendinous xanthomata</i> | 6 |
| <i>Arcus cornealis before age 45 years</i> | 4 |
| 4) LDL-C levels (without treatment): | |
| <i>LDL-C ≥ 325 mg/dL (≥ 8.5 mmol/L)</i> | 8 |
| <i>LDL-C 251-325 mg/dL (6.5-8.4 mmol/L)</i> | 5 |
| <i>LDL-C 191-250 mg/dL (5.0-6.4 mmol/L)</i> | 3 |
| <i>LDL-C 155-190 mg/dL (4.0-4.9 mmol/L)</i> | 1 |
| 5) DNA analysis: | |
| <i>Functional mutation in the LDLR, apoB, or PCSK9 genes</i> | 8 |
| <p>Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained:</p> <p>A 'definite' FH diagnosis requires > 8 points</p> <p>A 'probable' FH diagnosis requires 6-8 points</p> <p>A 'possible' FH diagnosis requires 3-5 points</p> | |

Table 29-10: ESC Recommendations for the management of patients with heterozygous familial hypercholesterolemia:

| | | |
|------------------------|--------------|--------------|
| Recommendations | Class | Level |
|------------------------|--------------|--------------|

(1) Exclusive of each other (i.e. maximum 6 points if both are present).

| | | |
|--|-----|---|
| <p><i>It is recommended that a diagnosis of FH is considered in:</i></p> <ul style="list-style-type: none"> - <i>Patients with CHD aged < 55 years for men and < 60 years for women,</i> - <i>People with severely elevated LDL-C [in adults > 190 mg/dL, in children > 150 mg/dL], and</i> - <i>People with relatives with premature fatal or non-fatal CVD,</i> - <i>People with relatives who have tendon xanthomas,</i> - <i>First-degree relatives of FH patients.</i> | I | C |
| <i>It is recommended that FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis.</i> | I | C |
| <i>Once the index case is diagnosed, family cascade screening is recommended.</i> | I | C |
| <p><i>It is recommended that FH patients:</i></p> <p><i>with ASCVD or who have another major risk factor are treated as very-high-risk, and that those with no prior ASCVD or other risk factors are treated as high-risk.</i></p> | I | C |
| <i>For FH patients with ASCVD who are at very high risk, treatment to achieve a $\geq 50\%$ reduction from baseline and an LDL-C < 55 mg/dL (< 1.4 mmol/L) is recommended. If goals cannot be achieved, a drug combination is recommended.</i> | I | C |
| <i>In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 55 mg/dL (< 1.4 mmol/L) should be considered.</i> | IIa | C |
| <i>Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.</i> | I | C |
| <i>In children, testing for FH is recommended from the age of 5 years, <u>or</u> earlier if HoFH is suspected.</i> | I | C |
| <i>Children with FH should be educated to adopt a proper diet and treated with a statin from 8-10 years of age. Goals for treatment should be LDL-C < 135 mg/dL at > 10 years of age.</i> | IIa | C |

Management in different clinical settings:

▪ Management of dyslipidemia in women:

Table 29-11: ESC recommendations for the Management of dyslipidaemia in women:

Statin treatment is recommended for primary prevention of ASCVD in high-risk women.

Statins are recommended for secondary prevention in women with the same indications and goals as in men.

Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy, or during the breastfeeding period. However, for severe FH patients, bile acid sequestrants (which are not absorbed) and/or LDL apheresis may be considered.

▪ Management of dyslipidemias in older people:

Table 29-12: ESC Recommendations for the Management of dyslipidemias in older people (> 65 years):

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.</i> | I | A |
| <i>Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤ 75 years.</i> | I | A |
| <i>Initiation of statin treatment for primary prevention in older people aged > 75 years may be considered, if at high-risk or above.</i> | IIb | B |
| <i>It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.</i> | I | C |

▪ Management of dyslipidemia in chronic kidney disease (CKD):

- In patients aged ≥ 50 years, CKD (GFR < 60 ml/min/1.73 m² or albuminuria) is associated with a 10-year risk of cardiovascular events $> 20\%$, and thus CKD should be considered a CAD equivalent and treated with a statin, regardless of LDL level and regardless of the presence of CAD (Kidney society guidelines).
- Paradoxically, at the extreme of CKD, patients with end-stage renal disease did not derive a benefit from statin therapy; this does not apply to patients with end-stage renal disease and established CAD.

| Table 29-13: ESC Recommendations for the treatment of dyslipidemias in chronic kidney disease: | | |
|--|------------|----------|
| <i>It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3-5 ⁽¹⁾ CKD are considered to be at high or very-high risk of ASCVD.</i> | I | A |
| <i>The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3-5 CKD.</i> | I | A |
| <i>In patients already on statins, ezetimibe, or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.</i> | IIa | C |
| <i>In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.</i> | III | A |

▪ **Management of dyslipidemia in metabolic syndrome and type 2 DM:**

| Table 29-14: Summary of dyslipidemia in metabolic syndrome and type 2 DM: |
|--|
| <i>Dyslipidemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and post-prandial TG, ApoB, and small dense LDL, and low HDL-C and ApoA1 levels.</i> |
| <i>Non-HDL-C or ApoB are good markers of TRLs and remnants, and are a secondary objective of therapy. Non-HDL-C < 100 mg/dL (< 2.6 mmol/L) and ApoB < 80 mg/dL are desirable in those at</i> |

(1) Defined as eGFR < 60 ml/min/1.73m² on two measurements more than 3 months apart

high-risk, and non-HDL-C < 85 mg/dL (< 2.2 mmol/L) and ApoB < 65 mg/dL in those at very high risk. For those at very high-risk with recurrent ASCVD events, goal of non-HDL-C < 70 mg/dL (< 1.8 mmol/L) and ApoB < 55 mg/dL may be considered.

Atherogenic dyslipidemia is one of the major risk factors for CVD in people with type 2 diabetes, and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

Table 29-15: ESC Recommendations for the treatment of dyslipidemias in diabetes mellitus:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), intensive lipid-lowering therapy, ultimately aiming at ≥ 50% LDL-C reduction and an LDL-C of < 55 mg/dL (<1.4 mmol/L) is recommended</i> | I | A |
| <i>In patients with type 2 DM > 40 years at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥ 50% LDL-C reduction and an LDL-C of < 70 mg/dL (1.8 mmol/L) is recommended.</i> | I | A |
| <i>Statins are recommended in patients with T1DM who are at high or very-high risk.</i> | I | A |
| <i>Intensification of statin therapy should be considered before the introduction of combination therapy.</i> | IIa | C |
| <i>If the goal is not reached, statin combination with ezetimibe should be considered.</i> | IIa | B |
| <i>Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or are not using adequate contraception.</i> | III | C |
| <i>Statin therapy may be considered in persons aged ≤ 40 years with type 1 or type 2 DM with evidence of TOD and/or an LDL-C level > 100 mg/dL (> 2.6 mmol/L), as long as pregnancy is not being planned.</i> | IIb | C |

▪ **Patients with ACS and patients undergoing PCI:**

| Table 29-16: ESC Recommendations for lipid-lowering therapy in very high-risk patients with ACS: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Lipid-lowering therapy in very high-risk patients with ACS: | | |
| <i>In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.</i> | I | A |
| <i>Lipid levels should be re-evaluated 46 weeks after ACS to determine whether a reduction of ≥50% from baseline and goal levels of LDL-C < 55 mg/dL (< 1.4 mmol/L) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.</i> | IIa | C |
| <i>If the LDL-C goal is not achieved after 46 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.</i> | I | B |
| <i>If the LDL-C goal is not achieved after 46 weeks despite maximal tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.</i> | I | B |
| <i>In patients with confirmed statin intolerance or in patients in whom a statin is contraindicated, ezetimibe should be considered.</i> | IIa | C |
| <i>For patients who present with an ACS and whose LDL-C levels are not at goal, despite already taking a maximally tolerated statin dose and ezetimibe, the addition of a PCSK9 inhibitor early after the event (during hospitalization for the ACS event if possible) should be considered.</i> | IIa | C |
| Lipid-lowering therapy in very high-risk patients undergoing PCI: | | |

| | | |
|--|------------|----------|
| <i>Routine pre-treatment or loading (on a background of chronic therapy) with a high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI.</i> | Ila | B |
|--|------------|----------|

| Table 29-17: ESC Recommendations for management of dyslipidemia in different clinical settings: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| Patients with prior ischemic stroke: | | |
| <i>Patients with a history of ischemic stroke or TIA are at very high-risk of ASCVD, particularly recurrent ischemic stroke, so it is recommended that they receive intensive LDL-C lowering therapy.</i> | I | A |
| Severe mental illness: | | |
| <i>It is recommended that SMIs are used as modifiers for estimating total ASCVD risk.</i> | I | C |
| <i>It is recommended that the same guidelines for the management of total ASCVD risk are used in patients with SMI as are used in patients without such disease.</i> | I | C |
| <i>It is recommended that in patients with SMI, intensified attention is paid to adherence to lifestyle changes and to compliance with drug treatment.</i> | I | C |
| Solid organ transplant patients: | | |
| <i>Statins should be considered as first-line agents in transplant patients. Initiation should be at low doses with careful up titration and with caution regarding potential drug drug interactions, particularly for patients on ciclosporin.</i> | Ila | B |
| <i>In patients who are intolerant of statins or those with significant dyslipidemia despite maximally tolerated statin treatment, alternative or additional therapy with ezetimibe may be considered.</i> | Ilb | C |
| Peripheral arterial disease (including carotid artery disease): | | |

| | | |
|---|------------|----------|
| <i>In patients with PAD, lipid-lowering therapy, including a maximum tolerated dose of statin, plus ezetimibe or a combination with a PCSK9 inhibitor if needed, is recommended to reduce the risk of ASCVD events.</i> | I | A |
| Chronic heart failure or valvular heart diseases | | |
| <i>Initiation of lipid-lowering therapy is not recommended in patients with HF in the absence of other indications for their use.</i> | III | A |
| <i>Initiation of lipid-lowering treatment in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use is not recommended.</i> | III | A |

N.B: Consider secondary causes of dyslipidemia in the proper setting: Hypothyroidism (↑ LDL), nephrotic syndrome (↑ LDL), uremia (↑ TG), alcohol abuse (↑ TG), and medications: β-blockers (↑ TG, ↓ HDL), thiazides (↑ LDL), contraceptive pills (↑ TG).

Inflammation and dyslipidemia:

Recent advances in basic science have established a fundamental role for low-degree chronic inflammation in mediating all stages of atherosclerosis, from initiation through progression and, ultimately, to the rupture of plaque and ensuing thrombotic complications of atherosclerosis.

During inflammatory processes, large numbers of acute-phase proteins have been identified, and several clinical studies have reported C-reactive protein to be the most useful serum marker of inflammation, even though it has poor specificity for any particular inflammation process, including atherosclerosis.

Important trials in dyslipidemia:

| Table 29-18: Clinical trials of dyslipidemia: | |
|---|---|
| Trial (date) | Summary |
| Statins: | |
| WOSCOPS (1995) | <p>Aim: To assess whether the use of pravastatin to men with hypercholesterolemia reduced the combined nonfatal MI and death from CAD.</p> <p>Study: 6,595 men, aged 45-64 years, with moderate hypercholesterolemia (a mean (\pm SD) cholesterol level of 272 (\pm 23) mg/dL) and no history of MI were randomly assigned to receive pravastatin (40 mg) or placebo. The average follow-up was 4.9 years. Pravastatin significantly reduced the incidence of MI and death from CV causes without adversely affecting the risk of death from non-cardiovascular causes in men.</p> |
| LIPID (1998) | <p>Aim: To compare the effects of pravastatin versus placebo in patients with coronary heart disease for the prevention of cardiac death.</p> <p>Study: 9,014 patients who were 31 to 75 years of age with history of MI or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg/dL were randomly assigned to pravastatin (40 mg daily) and to a placebo over a mean follow-up period of 6.1 years. Pravastatin reduced mortality from coronary heart disease and overall mortality, as compared with placebo, as well as the incidence of all prespecified CV events in patients with a history of MI or unstable angina who had a broad range of initial cholesterol levels.</p> |
| TNT (2005) | <p>Aim: To evaluate treatment of patients to a target LDL goal < 100 mg/dl among patients with stable coronary heart disease (CHD).</p> <p>Study: 10,001 patients with evident CHD and LDL-C < 130 mg/dL were randomly assigned to receive either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. Intensive lipid-lowering therapy with 80 mg of atorvastatin per day provides significant clinical benefit beyond that with 10 mg of atorvastatin per day. This occurred with a greater incidence of elevated aminotransferase levels.</p> |

| Ezetimibe: | |
|----------------------------|---|
| ENHANCE (2008) | <p>Aim: To determine whether the daily administration of ezetimibe in combination with simvastatin could reduce the progression of atherosclerosis in patients with familial hypercholesterolemia, as assessed by measurement of arterial intima-media thickness.</p> <p>Study: 720 patients with familial hypercholesterolemia were randomly assigned to daily therapy with simvastatin (80 mg) either with placebo or with ezetimibe (10 mg). Patients underwent ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. Combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL-C and C-reactive protein.</p> |
| SHARP (2011) | <p>Aim: To compare outcomes after randomization to simvastatin/ezetimibe or placebo in patients with CKD (eGFR < 30 ml/min).</p> <p>Study: 9,270 patients with advanced CKD (eGFR < 30 ml/min) were randomized in a ratio of 4:4:1 to ezetimibe/simvastatin (10/20 mg daily) versus placebo versus simvastatin (20 mg daily). After 1 year, patients initially allocated to simvastatin 20 mg daily alone (who formed a comparison group for the assessment of any early adverse effects of ezetimibe) were re-randomized to ezetimibe/simvastatin 10/20 mg daily versus placebo for the remainder of the scheduled study treatment period. Reduction of LDL-C with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.</p> |
| Niacin: | |
| AIM HIGH (2011) | <p>Aim: To assess whether niacin added to simvastatin to raise low levels of HDL-C is superior to simvastatin alone in reducing such residual risk.</p> <p>Study: 3,414 eligible patients were randomly assigned to receive extended-release niacin (1500-2000 mg/day) or placebo. All patients received simvastatin (40-80 mg/day), plus ezetimibe (10 mg/day, if needed) to maintain an</p> |

| | |
|-----------------------------|--|
| | <i>LDL-C of 40 to 80 mg/dL. There was no incremental clinical benefit from the addition of niacin to statin during a 36-month follow-up period, despite significant improvement in HDL-C and triglyceride levels.</i> |
| N-3 fatty acids: | |
| ORIGIN (2012) | <p>Aim: <i>To determine if long-term supplementation with n-3 fatty acids would reduce the rate of CV events in patients with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance are at increased risk for CV events.</i></p> <p>Study: <i>12,536 patients who were at high risk for CV events and had impaired fasting glucose, impaired glucose tolerance, or diabetes were randomly assigned to receive a 1-g capsule containing at least 900 mg of ethyl esters of n-3 fatty acids or placebo daily and to receive either insulin glargine or standard care. Daily 1 g of n-3 fatty acids did not reduce the rate of CV events in patients at high risk for CV events.</i></p> |
| REDUCE-IT (2018) | <p>Aim: <i>To assess the safety and benefit of icosapent ethyl in reducing CV events among patients with high triglycerides.</i></p> <p>Study: <i>8179 patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135-499 mg/dL and LDL-C level of 41-100 mg/dL. The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The risk of ischemic events, including CV death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo.</i></p> |
| EVAPORATE (2020) | <p>Aim: <i>To assess the efficacy of icosapent ethyl in reducing plaque burden among patients with known angiographic CAD on statins.</i></p> <p>Study: <i>68 patients had to have coronary atherosclerosis by coronary CT angiography (CCTA) on stable statin therapy with LDL-C levels 40-115 mg/dL, and persistently high triglyceride levels (135-499 mg/dL). Patients underwent an interim scan at 9 months and were followed for an additional 9 months with CCTA at 0, 9, and 18 months. Eligible patients were randomized to either icosapent ethyl 4 g/day or placebo. Icosapent ethyl 4 g/day reduces low attenuation plaque volume at 18 months among patients with known CAD, as assessed by cardiac CTA.</i></p> |

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|---------------------------------------|--|
| STRENGTH (2020) | <p>Aim: To evaluate the carboxylic acid formulation of EPA/DHA (omega-3 CA) among patients with dyslipidemia and high cardiovascular risk.</p> <p>Study: 13,078 participants with high cardiovascular risk, hypertriglyceridemia, and low levels of HDL-C were randomized to receive 4 g/d of omega-3 CA or corn oil, which was intended to serve as an inert comparator, in addition to usual background therapies, including statins. The addition of omega-3 CA to usual background therapies resulted in no significant difference in a composite outcome of MACE.</p> |
| PCSK9 inhibitors: | |
| ODYSSEY OUTCOME (2018) | <p>Aim: to assess the safety and efficacy of alirocumab among patients with recent ACS already on intensive or maximum-tolerated statin therapy.</p> <p>Study: 18,924 patients who had an ACS 1 to 12 months earlier, had LDL-C level ≥ 70 mg/dl, a non-HDL-C level ≥ 100 mg/dl, or an apolipoprotein B level ≥ 80 mg/dl, and were receiving high-intensity statin or the maximum tolerated dose. Those patients were randomly assigned to receive S.C alirocumab (75 mg) or matching placebo every 2 weeks. The primary endpoint was a composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. Alirocumab reduced the risk of recurrent ischemic CV events.</p> |
| FOURIER (2017) | <p>Aim: To evaluate the efficacy and safety of evolocumab among participants with elevated CV risk on statin therapy.</p> <p>Study: 27,564 patients with atherosclerotic CV disease and LDL-C ≥ 70 mg/dl who were receiving statin therapy were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary endpoint was the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Evolocumab on a background of statin therapy lowered LDL-C levels to a median of 30 mg/dl and reduced the risk of CV events.</p> |
| BANTING (2019) | <p>Aim: To assess the efficacy of 12 weeks of monthly evolocumab or placebo in lowering LDL-C in individuals with type 2 DM and hypercholesterolaemia or mixed dyslipidaemia and on a maximum-tolerated statin of at least moderate intensity.</p> |

| | |
|-----------------------------------|--|
| | <p>Study: 421 adult patients with type 2 diabetes, HbA_{1c} <10%, had been on stable pharmacological therapy for diabetes for ≥ 6 months and were taking a maximum-tolerated statin dose of at least moderate intensity were randomised to evolocumab 420 mg s.c. or placebo. In statin-treated individuals with type 2 diabetes and hypercholesterolaemia or mixed dyslipidaemia, evolocumab significantly reduced LDL-C and non-HDL-C. Favourable changes ($p < 0.05$) were observed in postprandial levels of chylomicrons, VLDL-C and LDL-C.</p> |
| BERSON (2019) | <p>Aim: To evaluate the lipid-lowering efficacy and safety of evolocumab combined with background atorvastatin in patients with type 2 DM and hyperlipidaemia or mixed dyslipidaemia.</p> <p>Study: 981 patients with type T2DM received atorvastatin 20 mg were randomised to evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) or placebo Q2W or QM. Co-primary endpoints were the percentage change in LDL-C from baseline to week 12 and from baseline to the mean of weeks 10 and 12. In patients with T2DM and hyperlipidaemia or mixed dyslipidaemia on statin, evolocumab significantly reduced LDL-C and other atherogenic lipids, was well tolerated, and had no notable impact on glycaemic measures.</p> |
| EBBINGHAUS (2017) | <p>Aim: To evaluate cognition using the Cambridge Neuropsychological Test Automated Battery (CANTAB) in patients who receive evolocumab.</p> <p>Study: The EBBINGHAUS study involved a subgroup of patients from the FOURIER trial. No significant difference in cognitive function was observed between either evolocumab or placebo over a median of 19 months.</p> |
| SPIRE 1 And SPIRE 2 (2017) | <p>Aim: To evaluate the efficacy and safety of bococizumab among subjects at elevated risk or with established CV disease on statin therapy.</p> <p>Study: The 27,438 patients in the combined trials were randomly assigned to receive bococizumab, a PCSK9 inhibitor (humanized antibody, >90% human; at a dose of 150 mg subcutaneously every 2 weeks) or placebo. Bococizumab had no benefit with respect to major adverse cardiovascular events in the trial involving lower-risk patients but did have a significant benefit in the trial involving higher-risk patients.</p> |
| ORION-9 (2019) | <p>Aim: To assess the safety and efficacy of inclisiran in lowering LDL-C among patients with heterozygous familial hypercholesterolemia (HeFH).</p> |

| | |
|--|---|
| | <p>Study: 482 adults who had heterozygous familial hypercholesterolemia were randomly assigned to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. Those who received inclisiran had significantly lower levels of LDL-C than those who received placebo, with an infrequent dosing regimen and an acceptable safety profile.</p> |
| <p>ORION-10 and ORION-11 (2020)</p> | <p>Aim: To assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for CV disease in whom LDL-C levels were elevated despite receiving statin therapy with or without additional lipid-lowering therapy.</p> <p>Study: 1561 patients with ASCVD (ORION-10 trial) and 1617 patients with ASCV or an ASCV risk equivalent (ORION-11 trial) who had elevated LDL-C levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The coprimary end points in each trial were the placebo-corrected percentage change in LDL-C level from baseline to day 510 and the time-adjusted percentage change in LDL-C level from baseline after day 90 and up to day 540. Reductions in LDL-C levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo.</p> |
| <p>Bempedoic acid:</p> | |
| <p>CLEAR Harmony (2019)</p> | <p>Aim: To assess the safety bempedoic acid in patients with high CV risk and elevated LDL-C that is not controlled by their current therapy.</p> <p>Study: 2230 patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Patients had to have an LDL cholesterol level of at least 70 mg/dL while they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive bempedoic acid or placebo. Bempedoic acid added to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significantly lower LDL cholesterol levels.</p> |

| | |
|-------------------------------------|---|
| CLEAR Wisdom (2019) | <p>Aim: To assess the safety and efficacy of bempedoic acid among patients already on intensive or maximum-tolerated statin therapy.</p> <p>Study: 779 patients with ASCVD or heterogeneous FH on maximum-tolerated statin therapy were randomized in a 2:1 fashion to either bempedoic acid 180 mg or placebo once daily for 52 weeks. All patients were on maximal tolerated statin and other lipid-lowering therapy. The trial showed that bempedoic acid is safe and effective in reducing LDL-C compared with placebo</p> |
| CETP inhibitors: | |
| Dal- OUTCOMES (2012) | <p>Aim: To evaluate the effects of dalcetrapib on cardiovascular risk among patients with a recent ACS.</p> <p>Study: 15,871 patients who had had a recent ACS were randomly assigned to receive the dalcetrapib (600 mg daily) or placebo, in addition to the best available evidence-based care. The primary efficacy end point was a composite of death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation. Dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent CV events.</p> |
| ACCELERATE (2017) | <p>Aim: To test the hypothesis that the addition of evacetrapib to standard medical therapy would result in a lower risk of death or complications from cardiovascular causes than placebo among patients with high-risk vascular disease.</p> <p>Study: 12,092 patients who had at least one of the following conditions: ACS within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or DM with CAD. Patients were randomly assigned to receive either evacetrapib (130 mg daily) or matching placebo, in addition to standard medical therapy. The primary efficacy end point was the first occurrence of any component of the composite of CV mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina. Evacetrapib did not result in a lower rate of cardiovascular events than placebo among patients with high-risk vascular disease.</p> |
| REVEAL (2017) | <p>Aim: To evaluate the CETP inhibitor anacetrapib compared with placebo among patients with stable atherosclerosis.</p> |

| | |
|----------------------------|--|
| | <p>Study: 30,449 adults with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy and who had a mean LDL cholesterol level of 61 mg/dl, a mean non-HDL cholesterol level of 92 mg/dl, and a mean HDL cholesterol level of 40 mg/dl. The patients were assigned to receive either 100 mg of anacetrapib once daily or matching placebo. The primary outcome was the first major coronary event, a composite of coronary death, MI, or coronary revascularization. Anacetrapib resulted in a lower major coronary events than the use of placebo.</p> |
| Fibrates: | |
| ACCORD-LIPID (2010) | <p>Aim: To investigate whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of CV disease in patients with type 2 DM who were at high risk for CV disease.</p> <p>Study: 5518 patients with type 2 diabetes who were being treated with simvastatin were randomly assigned to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes. The combination of fenofibrate and simvastatin did not reduce the rate of primary outcomes, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce CV risk in the majority of high-risk patients with type 2 DM.</p> |

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Chapter 30:

Cardiometabolism

DM is characterized by the presence of fasting hyperglycemia due to a reduction in insulin secretion (Type 1 diabetes) or insulin action (Type 2 diabetes). DM is important to diagnose because acute hyperglycemia can be symptomatic (weight loss, thirst, tiredness) and chronically is associated with the development of microvascular (eyes, nerves, kidneys) and macrovascular (heart, brain, peripheral vascular) disease.

In the clinic setting, HbA1c and fasting glucose are usually adequate to diagnose DM, however after acute illness such as in the coronary care setting, an oral glucose tolerance test may provide further information.

Diagnosis of diabetes:

Abnormal glucose metabolism has been divided into two clinical categories: diabetes and pre-diabetes, which are biochemical definitions:

- The diagnosis of **diabetes mellitus** depends on the detection of any of the following (WHO criteria):
 - HbA1C \geq 6.5% **or**
 - Fasting plasma glucose (FPG) \geq 126 mg/dl ⁽¹⁾ **or**
 - Oral glucose tolerance test (OGTT): 2-hr plasma glucose \geq 200 mg/dl following an oral glucose load equivalent to 75 g glucose ⁽²⁾ **or**
 - Symptoms of hyperglycemia **plus** non fasting plasma glucose of \geq 200 mg/dl.
- The diagnosis of **Pre-diabetes** depends on the detection of any of the following (WHO criteria):

(1) It should be noted that fasting is defined as no caloric intake for at least 8 h.

(2) OGTT should be performed under resting conditions, as exercise during the test can invalidate the results.

- HbA1C 6-6.4% ⁽¹⁾ **or**
- Fasting plasma glucose of 110-125 mg/dl (Impaired fasting glucose [IFG]) ⁽²⁾ **or**
- 2-hr plasma glucose of 140-200 mg/dl with FPG < 126 mg/dL (Impaired glucose tolerance [IGT]).

Prediabetes is a state indicating increased risk for development of diabetes. It is characterized by insulin resistance, hypertension and endothelial dysfunction.

N.B: In the absence of symptoms: To diagnose diabetes, you should have:

- Two tests of either FPG or random glucose levels in the diabetes range.
- The combination of HbA1c and fasting glucose in the diabetes range (second test is not required) ⁽³⁾.

| Table 30-1: ESC Recommendations for diagnosis of disorders of glucose metabolism: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Screening for diabetes is recommended in all individuals with CVD (including atherosclerotic CV disease, AF, and HF), using fasting glucose and/or HbA1c. | I | A |
| It is recommended that the diagnosis of diabetes is based on HbA1c and/or FPG or on an OGTT if still in doubt ⁽⁴⁾ . | I | B |

(1) ADA defined prediabetes with a wider range of HbA1C 5.7-6.4%.

(2) ADA defined prediabetes with glucose levels 100-125 mg/dL.

(3) If the two tests are discordant, the number in the diabetes range should be repeated or, preferably, an OGTT performed, which remains the gold standard for diagnosing diabetes in unclear cases.

(4) Stress hyperglycaemia should be suspected in the presence of high glucose levels and normal HbA1c.

Screening for diabetes:

It is generally agreed, however, that individuals in high-risk groups (those living with overweight or obesity, or having markers of insulin resistance, such as acanthosis nigricans or fatty liver disease) should be regularly screened, particularly after age 45 years. The ADA developed a relatively simple 7-point scoring system based on age, sex, weight, physical activity (PA), history of GDM, presence of hypertension, and family history of diabetes; it is advised that those scoring ≥ 5 are screened for diabetes.

Classifying diabetes:

After abnormal glucose metabolism is diagnosed, the next step is to ascertain the type of diabetes in order to start the appropriate therapies.

- **Type 1 diabetes:**

Type 1 diabetes constitutes 5-10% of individuals with diabetes and is secondary to destruction of pancreatic β -cells by an autoimmune process, with subsequent insulin deficiency.

Individuals aged < 35 years presenting with diabetes should be suspected of having T1DM, although this condition can occur at any age. A short history of osmotic symptoms accompanied by weight loss and raised glucose levels in a younger individual is highly suggestive of T1DM.

Antibody testing helps to confirm the diagnosis, although this can be negative in 5-10% of individuals with T1DM, while C-peptide helps to assess endogenous insulin production in unclear cases.

Pancreatic β -cell function can partially recover after the diagnosis of T1DM, and this can last several years, often referred to as the 'honeymoon period'. However, if this persists beyond 5 years, an alternative type of diabetes needs to be considered.

Of importance, the combination of T1DM with insulin resistance, which can be referred to as double diabetes (DD), increases the risk of vascular complications.

- **Type 2 diabetes:**

Type 2 diabetes is the most common cause of diabetes (90% of the diabetes population) and is usually caused by insulin resistance coupled with 'relative' insulin deficiency, resulting in raised glucose levels.

Individuals with T2DM can be asymptomatic and can be diagnosed after presenting with CV complications. Therefore, it is mandatory to screen all patients with CVD for the presence of diabetes.

- **Monogenic diabetes:**

This comprises many mutations that cause glucose mishandling. Monogenic diabetes should be suspected in the presence of a strong family history of abnormal glucose metabolism in an autosomal dominant manner (i.e. successive generations with diabetes at young age).

Patients diagnosed with diabetes before the age of 6 months and those not fitting the T1DM or T2DM profiles should be suspected of having monogenic diabetes.

- **Stress hyperglycemia:** Stress hyperglycemia without diabetes is associated with adverse in-hospital outcomes, and should be suspected in those with raised glucose levels during admission and normal HbA1c. Such individuals are best investigated using OGTT a few weeks after discharge to rule out DM.

- **Gestational diabetes (GDM):** defined as diabetes diagnosed in the 2nd or 3rd trimester of pregnancy that was not overt diabetes before gestation. While there is still no worldwide consensus regarding the best testing strategy, the 'one-step' 75 g OGTT is the preferred test. In women with GDM, repeat testing is required in the postpartum period to rule out persistent abnormal glucose metabolism.

Women with GDM will require lifelong annual diabetes screening given the high risk of developing diabetes. Also, evidence suggests that women with a history of GDM are at increased CV risk, even with normal post-partum glucose levels.

CV manifestations of diabetes:

- **Coronary artery disease:** DM increases the risk of coronary artery disease. In women, it blunts the cardiovascular benefit of the female gender. Patients with diabetes have a greater incidence of 3-vessel disease and more diffuse disease in both

proximal and distal coronary segments. Diabetic patients with ACS have increased rates of stroke, congestive HF and death during the index hospitalization.

- **Cerebrovascular disease:** DM increases risk of severe carotid atherosclerosis, stroke and stroke related dementia. It also increases the risk of stroke recurrence and mortality. The risk is more in young age and in women than in men.
- **Peripheral arterial disease:** DM increases the incidence of peripheral arterial disease. The disease typically involves the femoral, popliteal and infra-popliteal arteries. DM augments the likelihood of developing symptomatic forms of peripheral arterial disease particularly critical limb ischaemia with tissue loss. It is the most common cause of amputation.
- **Hypertension:** Hypertension is a common comorbidity of DM. It is often the result of underlying nephropathy in type I DM but is usually associated with overweight, unhealthy lifestyle and other metabolic risk factors in type 2 DM. Hypertension associated with DM increases the cardiovascular and renal risk. Efforts should be directed to block the renin-angiotensin system in those patients.
- **Heart failure:**
 - Increasing fasting glucose by 1 mmol/L increases the risk of heart failure by 14%.
 - Following an acute MI, the presence of DM increases the risk of developing new congestive HF. After an acute MI, diabetics show less compensatory increase in contractility of non-infracted myocardium than non-diabetics. This deficit persists overtime.
 - A specific cardiomyopathy (Diabetic cardiomyopathy) distinct from ischaemic injury does occur in diabetic patients. It is characterized by myofibril depletion, interstitial fibrosis, myocyte hypertrophy, microvascular basement membrane thickening and intramyocardial micro-angiopathy.

Possible contributing mechanisms include:

- Collagen accumulation leading to decreased myocardial compliance.
- Accumulation of advanced glycation end products (AGEs)-modified extracellular matrix causing diastolic dysfunction.
- Altered energy substrate supply and utilization
- Oxidative stress

- Abnormal myocardial calcium handling
- Endothelial dysfunction
- Deposition of intramyocardial fat (myocardial steatosis)
- Cardiac autonomic neuropathy
- Gene abnormalities
- **Atrial fibrillation:** Risk of AF and consequently stroke is increased in diabetics. Insulin resistance rather than hyperglycemia may account for the increased risk of AF. Guidelines recommend systemic anticoagulation for all diabetics with AF.
- **Thrombosis and coagulation:**
 - Intracellular platelet glucose concentration mirrors the extracellular environment and is associated with increased superoxide anion formation, protein kinase C (PKC) activity and decreased platelet derived NO.
 - Additionally, diabetics show increased expression of glycoproteins Ib and IIb/IIIa which enhances both platelet von-Willebrand factor and platelet-fibrin interactions.
 - Hyperglycemia impairs platelet calcium homeostasis, thereby alters platelet conformation, secretion and aggregation and thromboxane formation.
 - Blood coagulability is enhanced in diabetics. This is related to increased plasma coagulation factors (e.g. factor VII and thrombin), lesion-based coagulants (e.g. tissue factor), and atherosclerotic content of plasminogen activator inhibitor-1 as well as decreased endogenous anticoagulants (e.g. thrombomodulin and protein C).
- **Cardiovascular autonomic neuropathy (CAN):** This is a major complication of type I DM but is less expressed in patients with type 2 DM. The main consequences are dysfunctional heart rate control, abnormal vascular dynamics and cardiac denervation which become clinically overt as exercise intolerance, orthostatic hypotension, intraoperative cardiovascular morbidity and silent myocardial ischemia. CAN occurs in about 30% of diabetics and is associated with significantly higher mortality rate than in patients without CAN. The increased mortality rate is probably related to:
 - Higher prevalence of other complications such as diabetic nephropathy
 - Decreased perception of myocardial ischaemia

- Resting tachycardia due to parasympathetic denervation which increases myocardial O₂ demands
- Abnormal coronary blood flow regulation
- Increased prevalence of QT prolongation and QT dispersion
- **Sudden death:** DM is associated with an almost four-fold increased risk of sudden cardiac death. This may be related to the associated cardiac autonomic neuropathy, reduced heart rate variability, prolonged and increased dispersion of QT interval, LV dysfunction, hypoglycemia, and hyper- or hypokalemia.

CV risk assessment in patients with diabetes and prediabetes:

Individuals with T2DM are at a two- to four-fold higher risk of developing CVD during their lifetime alongside its manifestations CAD, stroke, HF, and AF, as well as PAD. Therefore, it is of utmost importance to screen patients with CVD for diabetes and to assess CV risk in individuals with diabetes, and evaluate them for CV and kidney disease.

When assessing CV risk in individuals with T2DM, it is important to consider medical and family history, symptoms, findings from examination, laboratory and other diagnostic test results, and the presence of ASCVD or severe TOD. Severe TOD is defined as:

- eGFR < 45 mL/min/1.73 m² irrespective of albuminuria or
- eGFR 45-59 mL/min/1.73 m² and microalbuminuria (urinary albumin-to-creatinine ratio [UACR] 30-300 mg/g; stage A2) or
- Proteinuria (UACR > 300 mg/g; stage A3) or
- Presence of microvascular disease in at least three different sites (e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy).

In patients aged ≥ 40 years with T2DM without ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm.

Individuals with T2DM should be categorized into different CV risk groups based on the following criteria:

- **Very high CV risk:** Patients with T2DM with:
 - Clinically established ASCVD or

- Severe TOD or
- 10-year CVD risk $\geq 20\%$ using SCORE2-Diabetes.
- **High CV risk:** Patients with T2DM not fulfilling the very high-risk criteria and a: 10-year CVD risk 10 to $< 20\%$ using SCORE2-Diabetes.
- **Moderate CV risk:** Patients with T2DM not fulfilling the very high-risk criteria and a: 10-year CVD risk 5 to $< 10\%$ using SCORE2-Diabetes.
- **Low CV risk:** Patients with T2DM not fulfilling the very high-risk criteria and a: 10-year CVD risk $< 5\%$ using SCORE2-Diabetes

| Table 30-2: ESC Recommendations for assessing CV risk in patients with type 2 diabetes: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended to screen patients with diabetes for the presence of severe TOD.</i> | I | A |
| <i>It is recommended to assess medical history and the presence of symptoms suggestive of ASCVD in patients with diabetes.</i> | I | B |
| <i>In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes ⁽¹⁾.</i> | I | B |

CV risk reduction in patients with diabetes: targets and treatments:

▪ Lifestyle management:

| Table 30-3: ESC Recommendations for lifestyle modifications in patients with diabetes with or without CV disease: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Weight reduction: | | |

(1) SCORE2-Diabetes refers to patients aged ≥ 40 years. In patients with T2DM without ASCVD and/or severe TOD, with age < 40 years, risk factors for ASCVD should be evaluated on an individual basis.

Weight loss of > 5% improves glycemic control, lipid levels, and BP in overweight and obese adults with T2DM. These effects can be achieved by improving energy balance and/or introducing obesity medications. Orlistat, naltrexone/bupropion, and phentermine/topiramate are each associated with achieving > 5% weight loss at 52 weeks. However, glucose-lowering agents such as GLP-1 RAs, the dual agonist tirzepatide, and SGLT2is also significantly reduce body weight. GLP-1 RAs has greater effect on weight reduction than SGLT2is.

| | | |
|--|---|---|
| <i>It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.</i> | I | A |
|--|---|---|

| | | |
|---|-----|---|
| <i>Glucose-lowering medications with effects on weight loss (e.g., GLP-1 RAs) should be considered in patients with overweight or obesity to reduce weight.</i> | IIa | B |
|---|-----|---|

| | | |
|--|-----|---|
| <i>Bariatric surgery should be considered for high and very high-risk patients with BMI ≥ 35 kg/m² when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss.</i> | IIa | B |
|--|-----|---|

Nutrition:

| | | |
|---|---|---|
| <i>It is recommended to adopt a Mediterranean or plant-based diet with high unsaturated fat content to lower cardiovascular risk.</i> | I | A |
|---|---|---|

physical activity/exercise:

| | | |
|---|---|---|
| <i>It is recommended to increase any physical activity (e.g. 10 min daily walking) in all patients with T2DM with and without CVD. Optimal is a weekly activity of 150 min of moderate intensity or 75 min of vigorous endurance intensity.</i> | I | A |
|---|---|---|

| | | |
|--|---|---|
| <i>It is recommended to adapt exercise interventions to T2DM-associated comorbidities, e.g. frailty, neuropathy, or retinopathy.</i> | I | B |
|--|---|---|

| | | |
|---|------------|----------|
| <i>It is recommended to introduce structured exercise training in patients with T2DM and established CVD, e.g. CAD, HFpEF, HFmrEF, HFrEF, or AF to improve metabolic control, exercise capacity and quality of life, and to reduce CV events.</i> | I | B |
| <i>It is recommended to perform resistance exercise in addition to endurance exercise at least twice a week.</i> | I | B |
| <i>The use of behavioural theory-based interventions, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback, should be considered to promote physical activity behaviour.</i> | IIa | B |
| <i>It should be considered to perform a maximally tolerated exercise stress test in patients with T2DM and established CVD before starting a structured exercise programme.</i> | IIa | C |
| <i>It may be considered to use wearable activity trackers to increase physical activity behaviour.</i> | IIb | B |
| Smoking cessation: | | |
| <i>It is recommended to stop smoking to reduce cardiovascular risk.</i> | I | A |
| <i>Nicotine replacement therapy, varenicline, and bupropion, as well as individual or telephone counselling, should be considered to improve smoking cessation success rate.</i> | IIa | B |

▪ **Glycaemic targets:**

- Reducing HbA1c decreases microvascular complications, particularly when achieving near-normal levels (HbA1c <7%), but the effects on macrovascular disease are more complex.
- Hypoglycaemia is associated with an increased risk of vascular events, explaining recent consensus advocating hypoglycaemic exposure at < 1% (i.e., <15 min/day) in individuals at high CV risk. The data suggest that the relationship between hypoglycemia events and risk of CV events (and vice versa) is most likely one of association rather than causation.
- Tighter glucose control initiated early in the course of DM in younger individuals leads to a reduction in CV outcomes over a 20-year timescale.

- Less-rigorous targets (HbA1c < 8.5%) should be considered in elderly patients on a personalized basis and in those with severe comorbidities or advanced CVD.

| Table 30-4: ESC Recommendations for glycemic control in patients with diabetes | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended to apply tight glycemic control (HbA1c < 7%) to reduce microvascular complications.</i> | I | A |
| <i>It is recommended to avoid hypoglycemia, particularly in patients with CVD.</i> | I | B |
| <i>It is recommended to individualize HbA1c targets according to comorbidities, diabetes duration, and life expectancy.</i> | I | C |
| <i>Tight glycemic control should be considered for reducing CAD in the long term, preferably using agents with proven CV benefit (SGLT2 inhibitors or GLP-1 RAs).</i> | IIa | B |

▪ **Glucose-lowering agents:**

• **Therapeutic agents that manage DM can be broadly characterized as belonging to one of five groups:**

- 1) Insulin providers (insulin, sulfonylureas, and meglitinides);
- 2) Insulin sensitizers (Biguanides [metformin] and Thiazolidinediones [pioglitazone and rosiglitazone]);
- 3) Incretin ⁽¹⁾-based therapies (Dipeptidyl peptidase 4 [DPP4] inhibitors and glucagon-like peptide-1 receptor agonists [GLP1-RAs]);
- 4) Gastrointestinal glucose absorption inhibitor (acarbose); and
- 5) Renal glucose reuptake inhibitors (SGLT2 inhibitors).

N.B: Effects of glucose-lowering drugs on weight:

(1) Incretins are gut peptides that are secreted after nutrient intake and augment the secretion of insulin from pancreatic beta cells.

The choice of glucose-lowering therapy is often influenced by effects on weight, when weight loss or avoiding weight gain is a priority.

- Insulins, sulphonylureas, and pioglitazone all cause weight gain;
- Metformin, acarbose, and the DPP-4 inhibitors are weight neutral or may result in small amounts of weight loss;
- SGLT2 inhibitors and GLP-1 RAs are associated with clinically meaningful weight loss, with weight effects of GLP-1 RAs being more pronounced than that of SGLT2 inhibitors.

Table 30-5: Main drugs used in the management of diabetes mellitus:

| Mechanism of action | Side-effects | Notes |
|---|--|--|
| Insulin: | | |
| Direct replacement for endogenous insulin | - Hypoglycemia - Weight gain - Lipodystrophy | Can be classified according to source (analogue, human sequence and porcine) and duration of action (short, immediate, long-acting) |
| Sulfonylurea: (e.g. gliclazide and glimepiride) | | |
| Cellular mechanism: Close K_{ATP} channels on pancreatic beta-cells Physiologic actions: Stimulate pancreatic beta cells to secrete insulin. | - Hypoglycemia - Weight gain - Hyponatremia (due to SIADH) | - Avoid in breast feeding and pregnancy. |
| Meglitinides: (e.g. repaglinide, nateglinide) | | |
| Like sulphonylureas, increase pancreatic insulin secretion as they bind to an ATP-dependent K^+ channel on the cell membrane of pancreatic beta cells. | - weight gain - hypoglycemia | often used for patients with an erratic lifestyle |
| Biguanides (Metformin) | | |
| Cellular mechanism: Activate AMP kinase, modulation of respiratory-chain complex 1. Physiologic actions: - ↑ insulin sensitivity | - GI upset (diarrhea) - Lactic acidosis | - First-line drug in the management of T2DM - Does not cause hypoglycemia or weight gain. - Cannot be used if eGFR of < 30 ml/min. - Stop during episodes of tissue hypoxia (e.g. MI) |

| | | |
|--|--|--|
| <ul style="list-style-type: none"> - ↓ hepatic gluconeogenesis - ↓ absorption of carbohydrates | | <ul style="list-style-type: none"> - Stop before IV contrast (e.g Angiography) and 2 days before general anaesthesia - Metformin reduces intestinal absorption of vit B12 and may lower serum B12 concentration. |
| Thiazolidinediones: (pioglitazone, Rosiglitazone) | | |
| <p>Cellular mechanism: Activate the nuclear transcription factor PPAR-γ</p> <p>Physiologic actions: Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake.</p> | <ul style="list-style-type: none"> - Weight gain - Fluid retention - ↑ risk of fracture | <ul style="list-style-type: none"> - Contraindicated in patients with a history of bladder cancer and congestive heart failure. - In patients who fail to show response to pioglitazone, stop it |
| DPP-4 inhibitors: (-gliptins) | | |
| <p>Cellular mechanism: Inhibit DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations.</p> <p>Physiologic actions: Increases incretin levels (by inhibiting its breakdown) which inhibit glucagon secretion and increase insulin secretion</p> | <ul style="list-style-type: none"> - Well tolerated but ↑ risk of pancreatitis | <ul style="list-style-type: none"> - Weight neutral - DPP-4 inhibitors require dose adjustment in patients with moderate or severe renal impairment (except Linagliptin) |
| Glucagon-like peptide (GLP-1) agonists: (-tides) | | |
| <p>Cellular mechanism: Activate GLP-1 receptors.</p> <p>Physiologic actions: Incretin mimetic which inhibits glucagon secretion and increase insulin secretion.</p> | <ul style="list-style-type: none"> - Nausea and vomiting - Pancreatitis | <p>Typically result in weight loss</p> <p>Stop exenatide if pancreatitis is diagnosed.</p> |
| Sodium-glucose co-transporter 2 (SGLT-2) inhibitors: | | |
| <p>Cellular mechanism: Inhibit SGLT-2 in the proximal nephron.</p> <p>Physiologic actions: Inhibits reabsorption of glucose in the proximal tubules</p> | <ul style="list-style-type: none"> - Urinary tract infection | <ul style="list-style-type: none"> - Typically result in weight loss - Low incidence of hypoglycemia |

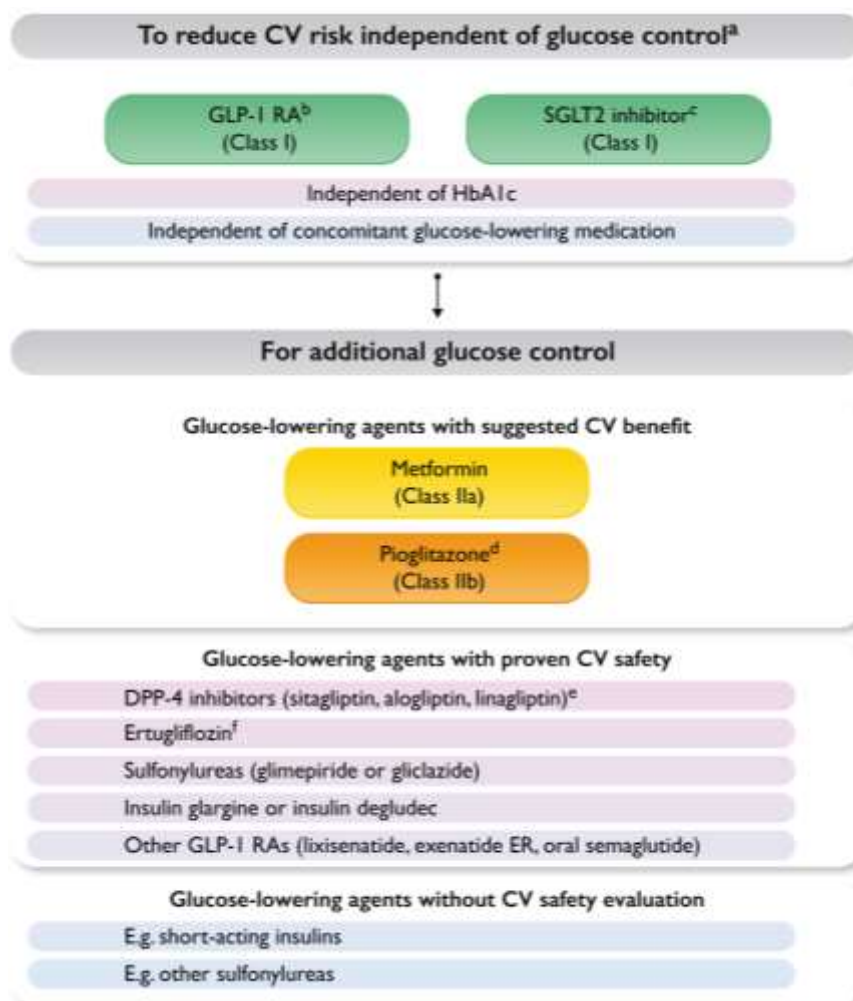


Figure 30-1: Glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk. A) In patients with ASCVD and T2DM, it is recommended to treat with a GLP-1 RA and/or SGLT2 inhibitor with proven benefit to reduce CV risk, independent of HbA1c and concomitant glucose-lowering medications. If additional glucose control is needed, treatment with metformin should be considered and treatment with pioglitazone may be considered. **B)** GLP-1 RAs with proven CV benefit: liraglutide, semaglutide s.c., dulaglutide, efpeglenatide. **C)** SGLT2 inhibitors with proven CV benefit: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin. **D)** Pioglitazone should not be used in patients with heart failure; the use in CKD requires caution as intravascular volume expansion and heart failure are common at reduced eGFR. **E)** DPP-4 inhibitors should not be used in patients on GLP-1 RAs. **F)** Ertugliflozin in the VERTIS CV trial showed safety with respect to three-point MACE but no benefit. **Source:** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.

CV effects of glucose-lowering drugs:

Glucose-lowering medications can be prescribed with two parallel, mutually exclusive intentions: **(i)** to improve CV outcomes and safety; and **(ii)** to control glucose. Therefore, glucose lowering drugs can be classified as following:

(A) Glucose-lowering medications with proven CV efficacy:

- **SGLT2 inhibitor:** SGLT2 inhibitors are a preferred glucose-lowering therapy for patients with T2DM with ASCVD, independent of glucose control considerations, and independent of background metformin use. A meta-analysis of the six SGLT2 inhibitor trials demonstrated a reduction in the primary ASCVD-based composite of time to first event of CV death, MI, or stroke (MACE). This was most apparent in patients with established ASCVD.
- **GLP-1 RAs:** Along with the SGLT2 inhibitors, GLP-1 RAs are a preferred glucose-lowering therapy for patients with T2DM and ASCVD, independent of glucose control considerations, and independent of background metformin use. The mechanisms of CV benefits of the GLP-1 RAs remain incompletely understood (driven by reduced risk of ASCVD-related events).
- **Pioglitazone:** Results from meta-analyses and observational studies have supported the efficacy of pioglitazone in persons with ASCVD. TZDs enhance fluid retention and the risk of peripheral oedema, especially with concomitant insulin use and in the context of kidney dysfunction. HF associated with TZDs appears to be attributable to expanded plasma volume, with no evidence of myocardial toxicity. TZDs induce weight gain due to adipose tissue expansion, but with weight redistributed predominantly to less metabolically active adipose tissue.

(B) Glucose-lowering medications with proven CV safety:

- **Dipeptidyl peptidase-4 (DPP-4) inhibitors:** Five randomized CV safety trials in populations with T2DM with or at high risk of ASCVD have demonstrated the CV safety of DPP-4 inhibitors.
- **Lixisenatide and exenatide:** Of the eight GLP-1 RAs evaluated in CVOTs, these are the only two agents that have demonstrated safety but not incremental efficacy.
- **Insulin:** Two basal insulins (Glargine and degludec) have been formally evaluated in dedicated CVOTs.

- **Glimepiride:** the long-lasting uncertainty about the CV safety of sulphonylureas may no longer be clinically relevant for glimepiride, at least in patients with a shorter duration of diabetes (like those enrolled in the CAROLINA trial; median duration of T2DM ~6 years).

(C) CV considerations of older glucose-lowering medications:

- **Metformin:** Despite its long history as the recommended first-line treatment of hyperglycaemia for patients with T2DM, there have been no dedicated randomized trials to rigorously assess the CV safety or efficacy of metformin. In meta-analyses of 13 randomized clinical trials evaluating the CV effects of metformin, none of the differences in assessed CV outcomes was statistically significant.
- **Sulphonylureas:** Excepting glimepiride, and gliclazide-modified release, dedicated CV safety assessments have not been conducted for the other sulphonylureas.

Table 30-6: ESC Recommendations for glucose lowering treatment in DM:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Type 2 DM with atherosclerotic cardiovascular disease: | | |
| <i>It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits (GLP-1 RA, and SGLT2 inhibitors) followed by agents with proven CV safety⁽¹⁾ over agents without proven CV benefit or proven CV safety.</i> | I | C |
| <i>SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.</i> | I | A |

(1) Metformin, pioglitazone, DPP-4 inhibitor (sitagliptin, alogliptin, linagliptin), glimepiride, gliclazide, insulin glargine, insulin degludec, ertugliflozin, lixisenatide, exenatide (extended release), oral semaglutide.

| | | |
|---|------------|----------|
| <i>GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.</i> | I | A |
| <i>If additional glucose control is needed, metformin should be considered in patients with T2DM and ASCVD.</i> | IIa | C |
| <i>If additional glucose control is needed, pioglitazone may be considered in patients with T2DM and ASCVD without HF.</i> | IIb | B |
| Type 2 DM without atherosclerotic cardiovascular disease: | | |
| <i>In patients with T2DM without ASCVD or severe TOD at low or moderate risk, treatment with metformin should be considered to reduce CV risk.</i> | IIa | C |
| <i>In patients with T2DM without ASCVD or severe TOD ⁽¹⁾ at high or very high risk, treatment with metformin may be considered to reduce CV risk.</i> | IIb | C |
| <i>In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk (using SCORE2-Diabetes) $\geq 10\%$, treatment with a SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.</i> | IIb | C |

▪ **Blood Pressure Control:**

- The BP goal of systolic BP is 120-130 mmHg in patients with diabetes, with lower SBP acceptable if tolerated until the age of 69 years. In patients aged ≥ 70 years, SBP 130-139 mmHg is recommended.
DBP treatment target < 80 mmHg is recommended for all treated patients.
- Evidence strongly supports the inclusion of ACEI, or an ARB in patients who are intolerant to ACEI, particularly in patients with evidence of end-organ damage (albuminuria and LVH).

(1) Severe TOD defined as $eGFR < 45$ mL/min/1.73 m²; or $eGFR 45-59$ mL/min/1.73 m² and microalbuminuria (UACR 30-300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g., microalbuminuria (stage A2) plus retinopathy plus neuropathy].

- Controlling BP often requires multiple drug therapy with an RAS inhibitor and a CCB or diuretic, while the combination of an ACE-I with an ARB is not recommended. Consider beta-blockers at any treatment step when specifically indicated, e.g., HF, angina, post-MI, AF, or younger women with or planning pregnancy.
- In apparent resistant (including MRA-resistant) hypertension in patients with HFpEF, sacubitril/valsartan helped to better control BP compared with valsartan.
- In pre-DM, the risk of new-onset DM is lower with RAAS blockers than with beta-blockers or diuretics.
- GLP1-RAs have shown evidence of a slight, but significant, BP decrease, partly due to weight loss.
- SGLT2 inhibitors induced a larger BP decrease without heart rate changes.

| Table 30-7: ESC Recommendations for the management of blood pressure in patients with diabetes: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Screening for hypertension: | | |
| <i>Regular BP measurements are recommended in all patients with diabetes to detect and treat hypertension to reduce CV risk.</i> | I | A |
| Treatment targets: | | |
| <i>Anti-hypertensive drug treatment is recommended for people with diabetes when office BP is \geq 140/90 mmHg.</i> | I | A |
| <i>It is recommended to treat hypertension in patients with diabetes in an individualized manner. The BP goal is to target SBP to 130 mmHg and $<$ 130 mmHg if tolerated, but not $<$ 120 mmHg. In older people (age $>$ 65 years), it is recommended to target SBP to 130– 139 mmHg.</i> | I | A |
| <i>An on-treatment SBP target of $<$130 mmHg may be considered in patients with diabetes at particularly high risk of a cerebrovascular event to further reduce their risk of stroke.</i> | IIb | B |
| Treatment and evaluation: | | |

| | | |
|---|------------|----------|
| <i>Lifestyle changes (weight loss if overweight, physical activity, alcohol restriction, sodium restriction, increased consumption of vegetables, using low-fat dairy products) are recommended in patients with diabetes and hypertension.</i> | I | A |
| <i>It is recommended to initiate treatment with a combination of a RAS inhibitor and a CCB or thiazide/thiazide-like diuretic.</i> | I | A |
| <i>Home BP self-monitoring should be considered in patients with diabetes on anti-hypertensive treatments to check that BP is appropriately controlled.</i> | Ila | B |
| <i>24 h ambulatory blood pressure monitoring should be considered to assess abnormal 24 h BP patterns, including nocturnal hypertension and reduced or reversed nocturnal BP dipping, and to adjust anti-hypertensive treatment.</i> | Ila | B |

▪ **Lipids Control:**

- A cluster of lipid and apolipoprotein abnormalities accompanies DM. The core components are moderately elevated plasma triglyceride (TG), TG-rich lipoprotein (TRL), and TRL cholesterol levels, normal-to-mildly elevated LDL-C, and low HDL-C. In well-controlled T1DM, HDL-C levels tend to be normal (or even slightly elevated), as do serum triglyceride levels.
- Currently, statins remain state-of-the-art therapy in lipid lowering treatment in patients with DM. Similar benefits were seen in both T1DM and T2DM. This beneficial effect outweighs the potential diabetogenic effect of these drugs, estimated as a 9% increased risk of incident diabetes, especially in older patients and in patients already at risk of developing diabetes.
- In both T1DM and young-onset T2DM, there is a paucity of evidence to indicate the age at which statin therapy should be initiated and in the absence of specific indications, it seems reasonable to delay statin therapy in asymptomatic DM patients until the age of 30. Below this age, statin therapy should be managed on a case-by case basis taking into account the presence of microalbuminuria, end-organ damage, and ambient LDL-C levels.
- Ezetimibe or a PCSK9 inhibitor on top of a statin -or alone in case of documented intolerance to statins- further contribute to LDL-C reduction in patients with DM, thus improving CV outcomes.

Table 30-8: ESC Recommendations for the management of dyslipidemia in patients with diabetes:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Lipid targets: | | |
| <i>In patients with T2DM at moderate CV risk, an LDL-C target of < 2.6 mmol/L (< 100 mg/dL) is recommended.</i> | I | A |
| <i>In patients with T2DM at high CV risk, an LDL-C target of < 1.8 mmol/L (< 70 mg/dL) and LDL-C reduction of at least 50% is recommended.</i> | I | A |
| <i>In patients with T2DM at very high CV risk, an LDL-C target of < 1.4 mmol/L (< 55 mg/dL) and LDL-C reduction of at least 50% is recommended.</i> | I | B |
| <i>In patients with T2DM, a secondary goal of a non-HDL-C target of < 2.2 mmol/L (< 85 mg/dL) in very high CV risk patients and < 2.6 mmol/L (< 100 mg/dL) in high CV risk patients is recommended.</i> | I | B |
| Lipid-lowering treatment: | | |
| <i>Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.</i> | I | A |
| <i>A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.</i> | I | A |
| <i>If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.</i> | I | B |
| <i>If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.</i> | IIa | C |
| <i>High-dose icosapent ethyl (2 g b.i.d.) may be considered in combination with a statin in patients with hypertriglyceridemia (TG 150-499 mg/dL, according to REDUCE-IT trial).</i> | IIb | B |

▪ **Antithrombotic therapy:**

- Patients with DM and symptomatic CVD should be treated no differently to patients without DM.
- In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended. Studies reported a 12% reduction in CVD outcomes with aspirin, but a significant increase in major bleeds (ARRIVE and ASCEND trials). Therefore, aspirin may be considered in in patients with diabetes with asymptomatic ASCVD (including documented CAD confirmed by imaging) and a higher CV risk, the net benefit of platelet inhibition by ASA may be higher and thus, therapy needs to be individualized.

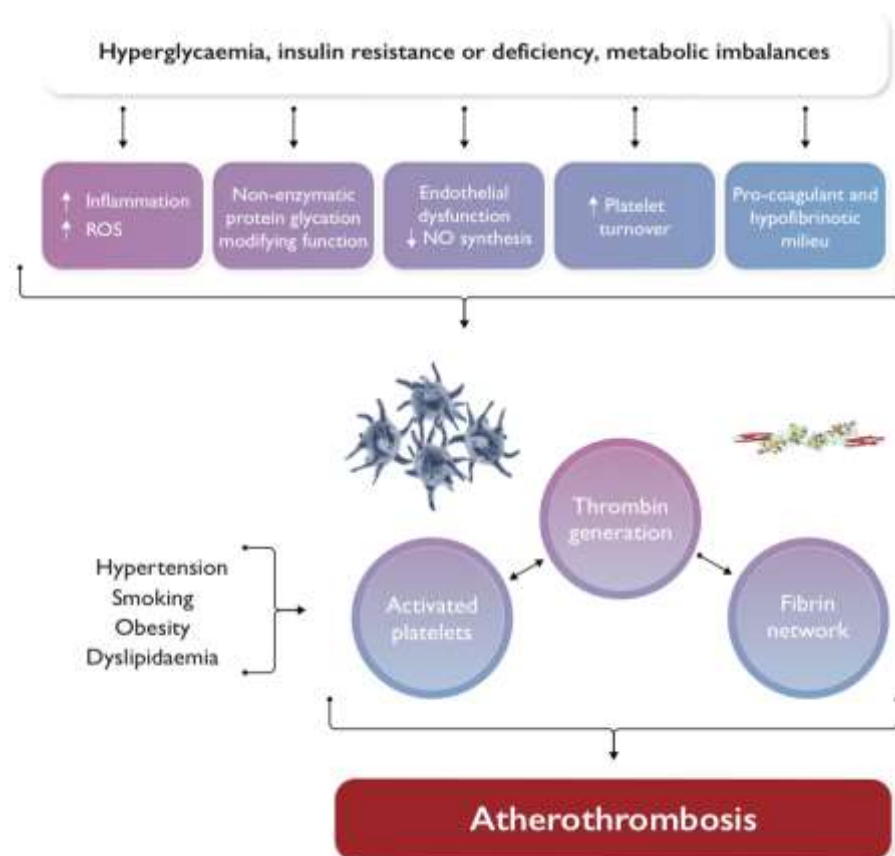


Figure 30-2: Mechanisms contributing to altered platelet activation and atherothrombosis in patients with diabetes. The figure depicts the major determinants contributing to platelet activation leading to atherothrombosis in patients with diabetes. An inflammatory environment, metabolic changes, endothelial dysfunction and altered platelet turnover result in a platelet population characterized by enhanced activation, increased thrombin generation, and suppression of the fibrinolytic system. Thrombin release by platelets and de novo generation through activation of the coagulation pathway further amplify platelet activation and result in fibrin network formation, thus playing a pivotal role in the increased risk of thrombosis in individuals with diabetes. **Source:** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.

Table 30-9: ESC Recommendations for management of antithrombotic therapy in diabetes:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Patients with diabetes without a history of symptomatic ASCVD or revascularization: | | |
| <i>In adults with T2DM without a history of symptomatic ASCVD or revascularization, ASA (75– 100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications ⁽¹⁾.</i> | IIb | A |
| Patients with ACS or CCS without indications for long-term OAC: | | |
| <i>ASA at a dose of 75–100 mg o.d. is recommended in patients with diabetes and previous MI or revascularization (CABG or stenting).</i> | I | A |
| <i>In patients with ACS and diabetes who undergo PCI, a P2Y12 receptor inhibitor (ticagrelor or prasugrel) is recommended in addition to ASA (75–100 mg o.d.), maintained over 12 months.</i> | I | A |
| <i>Clopidogrel 75 mg o.d. following appropriate loading (e.g. 600 mg or at least 5 days already on maintenance therapy) is recommended in addition to ASA for 6 months following coronary stenting in patients with CCS, irrespective of stent type, unless a shorter duration is indicated due to the risk or occurrence of life-threatening bleeding.</i> | I | A |
| <i>Clopidogrel is recommended as an alternative in case of ASA intolerance.</i> | I | B |
| <i>In patients with diabetes and ACS treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resuming a P2Y12 receptor inhibitor as soon as deemed safe after surgery and continuing it up to 12 months is recommended.</i> | I | C |

(1) High risk of bleeding due to gastrointestinal hemorrhage or peptic ulcer within the previous 6 months, active hepatic disease (such as cirrhosis, active hepatitis), or history of ASA allergy.

| | | |
|--|------------|----------|
| <i>Prolonging DAPT beyond 12 months after ACS should be considered for up to 3 years in patients with diabetes who have tolerated DAPT without major bleeding complications ⁽¹⁾.</i> | Ila | A |
| <i>Adding very low-dose rivaroxaban (2.5 mg b.i.d.) to low-dose ASA for long-term prevention of serious vascular events should be considered in patients with diabetes and CCS or symptomatic PAD without high bleeding risk.</i> | Ila | B |
| Patients with ACS or CCS with indications for long-term OAC: | | |
| <i>In patients with AF and receiving antiplatelet therapy, eligible for anticoagulation, and without a contraindication, NOACs are recommended in preference to a VKA.</i> | I | A |
| <i>In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, triple therapy with low-dose ASA, clopidogrel, and an OAC is recommended for at least 1 week, followed by dual therapy with an OAC and a single, oral, antiplatelet agent.</i> | I | A |
| <i>In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC should be considered up to 1 month if the thrombotic risk outweighs the bleeding risk in the individual patient.</i> | Ila | C |
| <i>In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC up to 3 months may be considered if the thrombotic risk outweighs the bleeding risk in the individual patient.</i> | Ilb | C |
| Gastric protection in patients with diabetes taking antithrombotic drugs: | | |
| <i>When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.</i> | I | A |
| <i>When a single antiplatelet or anticoagulant drug is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding, considering the bleeding risk of the individual patient.</i> | Ila | A |
| <i>When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.</i> | III | B |

(1) In case of ticagrelor, a reduced dose (60 mg b.i.d.) should be used.

▪ **Multifactorial approaches:**

- Combined reduction in HbA1c, SBP, and lipids decreases CV events by 75%.
- Patients who cluster conventional cardiovascular risk factors (lipids, smoking, hypertension, obesity, dysglycemia) have an elevated risk of cardiovascular events which is markedly reduced by managing each risk factor to goal. Studies indicate low rates of conversion to goal for most targets and it is important to achieve compliance through patient education and support networks.

| Table 30-10: Summary of treatment targets for the management of patients with diabetes | |
|--|--|
| Risk factor | Target |
| BP | <ul style="list-style-type: none"> • Target SBP 130 mmHg for most adults, < 130 mmHg if tolerated, but not < 120 mmHg • Less-stringent targets, SBP 130 - 139 in older patients (aged > 65 years) |
| Glycaemic control: HbA1c | <ul style="list-style-type: none"> • HbA1c target for most adults is < 7.0% (< 53 mmol/mol) • More-stringent HbA1c goals of < 6.5% (48 mmol/mol) may be suggested on a personalized basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment. • Less-stringent HbA1c goals of < 8% (64 mmol/mol) or ≤ 9% (75 mmol/mol) may be adequate for elderly patients. |
| Lipid profile: LDL-C | <ul style="list-style-type: none"> • In patients with DM at very high CV risk, a target LDL-C to < 55 mg/dL (< 1.4 mmol/L) • In patients with DM at high risk, target LDL-C to < 70 mg/dL (< 1.8 mmol/L) • In patients with DM at moderate CV risk, aim for an LDL-C target of < 100 mg/dL (< 2.5 mmol/L) |
| Platelet inhibition | In DM patients at high/very high CV risk |

| | |
|--------------------------|--|
| Smoking | <i>Cessation obligatory</i> |
| Physical activity | <i>Moderate-to-vigorous, ≥ 150 min/week, combined aerobic and resistance training.</i> |
| Weight | <i>Aim for weight stabilization in overweight or obese patients with DM, based on calorie balance, and weight reduction in subjects with IGT, to prevent the development of DM.</i> |
| Dietary habits | <i>Reduction of caloric intake is recommended in obese patients with T2DM to lower body weight; there is no ideal percentage of calories from carbohydrate, protein, and fat for all people with DM.</i> |

Management of coronary artery disease:

- **Chronic Coronary Syndrome and DM:**

- Diabetes is a well-established risk factor for ischemic heart disease (IHD), and CAD accounts for 40–80% of deaths in patients with T2DM. Approximately 20-30% of patients with CAD have known DM, and up to 70% of the remainder have newly detected DM or IGT when investigated with an OGTT.
- Patients with CAD, without known glucose abnormalities, should have their glycemic state evaluated.
- Screening for asymptomatic CAD in diabetes remains controversial.
- **Management:** The comprehensive management of patients with diabetes and established CAD should start with a healthy lifestyle and reducing or eliminating modifiable risk factors such as obesity, hypertension, or dyslipidemia.
 - Glucose-lowering medication: SGLT2 inhibitors and/or GLP-1 RAs are recommended in patients with T2DM and CAD to reduce CV events.
 - Other medications: Symptom relief might then be achieved by increasing myocardial oxygen supply with long-acting nitrates or CCBs, or by decreasing oxygen demand with the help of beta-blockers, non-dihydropyridine CCBs, ranolazine, or ivabradine.

Note that none of these medications improves mortality or the rate of ischaemic events. Beta-blockers with a simultaneous vasodilatory effect (e.g. carvedilol, nebivolol, labetalol) may be preferred due to their neutral or positive metabolic impact.

- Revascularization: in patients with diabetes, the indications for myocardial revascularization are the same as those in patients without diabetes. Given the current knowledge, in patients with diabetes and multivessel disease, CABG with arterial grafts is preferred over complex PCI, providing that patient characteristics (e.g. frailty, cerebrovascular disease) are considered. PCI is acceptable for patients with less-extensive disease (i.e. single-vessel disease or two-vessel disease not involving the LAD, and those with SYNTAX Score ≤ 22).
- Intensive secondary prevention is indicated in patients with DM and CAD. Antiplatelet drugs are the cornerstone of secondary CV prevention.
- In high-risk patients, the combination of low-dose rivaroxaban and aspirin may be beneficial for CAD.
- In patients with DM and multivessel CAD, suitable coronary anatomy for revascularization, and low predicted surgical mortality, CABG is superior to PCI.

- **Acute coronary syndromes and diabetes:**

- Among patients presenting with STEMI, ~25% have a history of diabetes and more than 40% show a previously undiagnosed T2DM or pre-diabetes.
- Patients with diabetes more often present with non-typical symptoms compared with those without diabetes, and this impacts prompt diagnosis and treatment.
- Patients with diabetes frequently have multivessel disease and multiple coronary lesions, with a higher percentage of highly vulnerable plaques associated with impaired microvasculature vasodilation.
- Patients with ACS and hyperglycemia on admission to hospital have a higher risk of death than patients with ACS without hyperglycemia, irrespective of diabetes status. Mortality correlates more strongly to the blood glucose level than to the presence of diabetes. Thus, early assessment of blood glucose level is strongly recommended in all subjects, although there is insufficient evidence that intensive glycemic control improves prognosis.

- Considering all evidence, it is best to attempt moderately tight glycemic control while avoiding hypoglycemia in the early hours of ACS. Continuous insulin infusion should be limited to cases where the optimal glycemic control cannot be achieved otherwise; blood glucose level should be maintained < 200 mg/dL or < 180 mg/dL according to some recommendations.

Table 30-11: ESC Recommendations for the management of patients with diabetes and acute or chronic coronary syndromes:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Revascularization: | | |
| <i>It is recommended that similar revascularization techniques are implemented (e.g. the use of DES and the radial approach for PCI, and the use of the left internal mammary artery as the graft for CABG) in patients with and without diabetes.</i> | I | A |
| <i>Myocardial revascularization in CCS is recommended when angina persists despite treatment with anti-anginal drugs or in patients with a documented large area of ischemia (> 10% LV).</i> | I | A |
| <i>Complete revascularization is recommended in patients with STEMI without cardiogenic shock and with multivessel CAD.</i> | I | A |
| <i>Complete revascularization should be considered in patients with NSTEMI-ACS without cardiogenic shock and with multivessel CAD.</i> | IIa | C |
| <i>Routine immediate revascularization of non-culprit lesions in patients with MI and multivessel disease presenting with cardiogenic shock is not recommended.</i> | III | B |
| Glycemic control in ACS: | | |
| <i>It is recommended to assess glycemic status at initial evaluation in all patients with ACS.</i> | I | B |
| <i>It is recommended to frequently monitor blood glucose levels in patients with known diabetes or hyperglycemia (defined as glucose levels ≥ 11.1 mmol/L or ≥ 200 mg/dL).</i> | I | C |

Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycemia, while episodes of hypoglycemia should be avoided.

Ila

C

Heart failure and diabetes:

- Patients with pre-DM and DM are at increased risk of developing HF.
- Patients with DM are at greater risk of HFrEF, HFmrEF or HFpEF; conversely, HF increases the risk of DM.
- Major causes of HF in diabetes are IHD, hypertension, direct or indirect effects of hyperglycaemia, and obesity and related factors on the myocardium.
- Patients with T2DM develop chronic HF more often and earlier in life than those without T2DM, with an incremental risk inversely associated with age (higher absolute HF risk in elderly patients without DM).
- The coexistence of DM and HF imparts a higher risk of HF hospitalization, all-cause death, and CV death. CV mortality is 50-90% higher in patients with HF and DM, regardless of HF phenotype.
- To predict the HF risk among outpatients with T2DM, the **WATCH-DM** (Weight [BMI], Age, Hypertension, Creatinine, HDL-C, Diabetes control [fasting plasma glucose], QRS duration, MI, and CABG) risk score has been developed. Each increment of 1 unit in the risk score is associated with a 24% higher HF risk within 5 years.
- Guideline-based medical and device therapies are equally effective in patients with and without DM; as renal dysfunction and hyperkalemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g., RAAS blockers) are advised.

Table 30-12: ESC Recommendations for the treatment of heart failure in patients with diabetes:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Evaluating for HF: | | |
| <i>If HF is suspected, it is recommended to measure BNP/NT-proBNP.</i> | I | B |
| <i>Systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter in all patients with diabetes.</i> | I | C |

| Diagnostic tests in all patients with suspected HF: | | |
|--|---|---|
| <ul style="list-style-type: none"> ○ 12-lead ECG is recommended. ○ Transthoracic echocardiography is recommended. ○ Chest radiography (X-ray) is recommended. ○ Routine blood tests for comorbidities are recommended, including full blood count, urea, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT). | I | C |
| Treatment indicated in patients with HFrEF (NYHA class II-IV) and diabetes: | | |
| <p><i>To reduce the risk of HF hospitalization and death in patients with HFrEF and diabetes:</i></p> <ul style="list-style-type: none"> ○ SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended. ○ Sacubitril/valsartan or an ACE-I is recommended. ○ Beta-blockers (Sustained-released metoprolol succinate, carvedilol, bisoprolol, and nebivolol) are recommended. ○ MRAs are recommended. | I | A |
| <i>An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.</i> | I | B |
| <i>Device therapy with an ICD, CRT-P, or CRT-D is recommended in patients with diabetes, as in the general population with HFrEF.</i> | I | A |
| <i>ARBs are recommended in symptomatic patients with HFrEF and diabetes who do not tolerate sacubitril/valsartan or ACE-Is, to reduce the risk of HF hospitalization and CV death.</i> | I | A |
| <i>Diuretics are recommended in patients with HFrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.</i> | I | C |

| | | |
|---|------------|----------|
| <i>Ivabradine should be considered to reduce the risk of HF hospitalization and CV death in patients with HFrEF and diabetes in sinus rhythm, with a resting heart rate ≥ 70 b.p.m., who remain symptomatic despite treatment with beta-blockers (maximum tolerated dose), ACE-Is/ARBs, and MRAs.</i> | IIa | B |
| <i>Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF $\leq 35\%$ or with LVEF $< 45\%$ combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.</i> | IIa | B |
| <i>Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.</i> | IIb | B |
| HF treatments in patients with diabetes and LVEF > 40%: | | |
| <i>Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.</i> | I | A |
| <i>Diuretics are recommended in patients with HFpEF or HFmrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.</i> | I | C |

- **Safety profile of glucose-lowering agents in patients with HF and DM:**

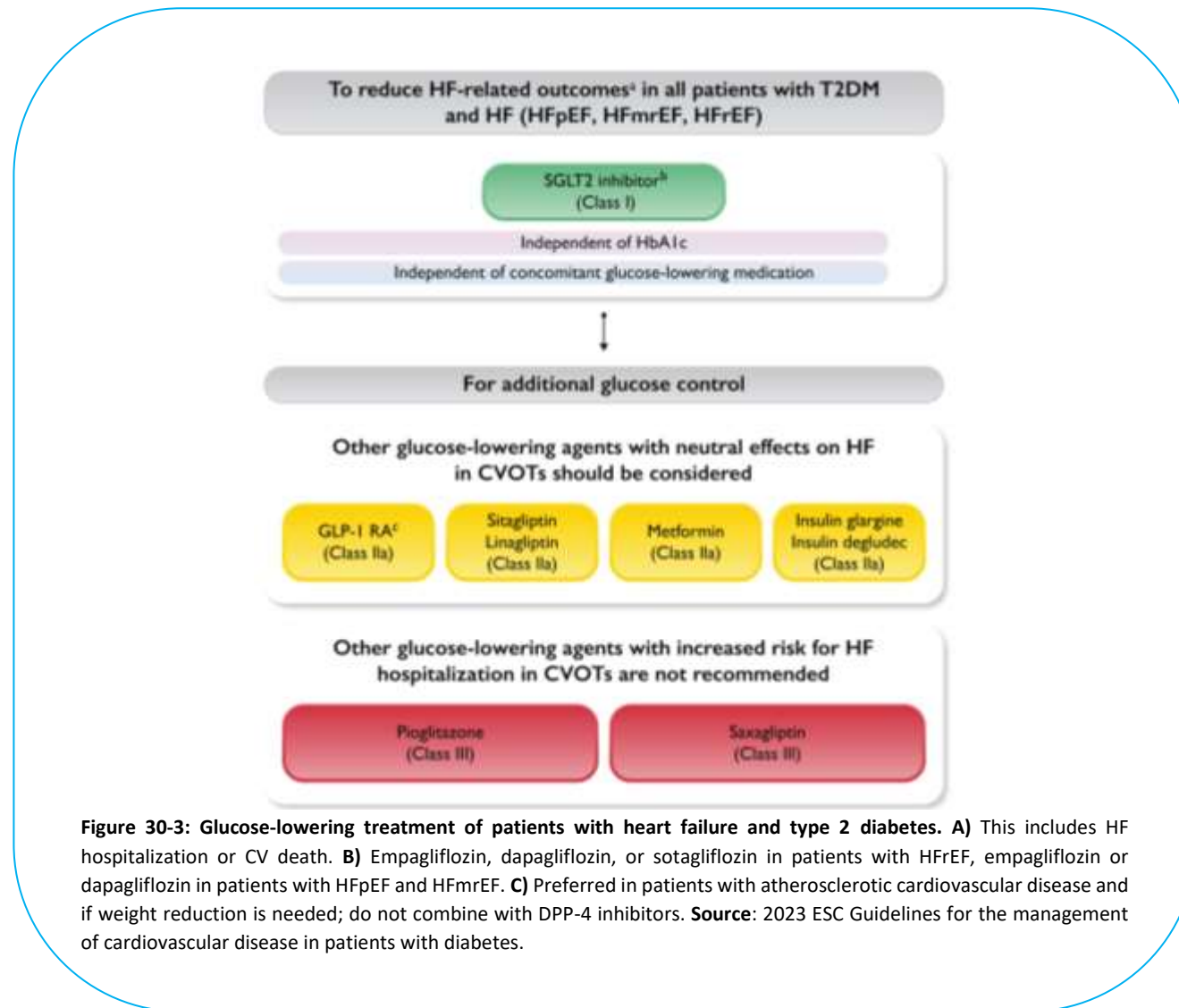


Figure 30-3: Glucose-lowering treatment of patients with heart failure and type 2 diabetes. **A)** This includes HF hospitalization or CV death. **B)** Empagliflozin, dapagliflozin, or sotagliflozin in patients with HFrEF, empagliflozin or dapagliflozin in patients with HFpEF and HFmrEF. **C)** Preferred in patients with atherosclerotic cardiovascular disease and if weight reduction is needed; do not combine with DPP-4 inhibitors. **Source:** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.

Table 30-13: ESC Recommendations for glucose-lowering medications in patients with type 2 diabetes with and without heart failure:

| Recommendations | Class | Level |
|---|--------------|--------------|
| To reduce HF hospitalization in patients with type 2 diabetes with or without existing HF: | | |
| <i>SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, or sotagliflozin) are recommended in patients with T2DM with multiple ASCVD risk factors or established ASCVD to reduce the risk of HF hospitalization.</i> | I | A |
| <i>SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce the risk of HF hospitalization and CV death.</i> | I | A |
| <i>Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF > 40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.</i> | I | A |
| Additional glucose-lowering agents with safety demonstrated for HF hospitalization in patients with type 2 DM if additional glucose control is needed: | | |
| <i>GLP-1 RAs (lixisenatide, liraglutide, semaglutide, exenatide ER, dulaglutide, efpeglenatide) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.</i> | IIa | A |
| <i>DPP-4 inhibitors (sitagliptin and linagliptin) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.</i> | IIa | A |
| <i>Basal insulins (glargine and degludec) have a neutral effect on the risk of HF hospitalization and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.</i> | IIa | B |
| <i>Metformin should be considered for glucose-lowering treatment in patients with T2DM and chronic stable HF.</i> | IIa | B |
| Glucose-lowering agents with an increased risk of HF hospitalization in patients with type 2 DM: | | |

| | | |
|--|-----|---|
| <i>Pioglitazone is associated with an increased risk of incident HF in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).</i> | III | A |
| <i>The DPP-4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).</i> | III | B |
| Special consideration: | | |
| <i>It is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit.</i> | I | C |

Arrhythmias: AF, ventricular arrhythmias, and sudden cardiac death:

- **DM and AF:**

- DM is an independent risk factor for AF, especially in young patients. Diabetes duration has also been associated with AF; each year with diabetes conferred a 3% increase in the risk of AF.
Screening for AF should be recommended for patients with DM aged > 65 years by pulse palpation or wearable devices. AF should always be confirmed by ECG.
- Atrial premature beats are also common in patients with DM and may predispose to the development of AF.
- When DM and AF coexist, there is a substantially higher risk of all cause death, CV death, stroke, and HF. Anticoagulation is recommended in all patients with DM and AF.

- **DM and Ventricular arrhythmia:**

- PVCs and NSVT are common in patients with DM. In patients with DM with frequent symptomatic PVCs or episodes of NSVT, the presence of underlying structural heart disease should be examined by exercise ECG, echocardiography, coronary angiography, or MRI.
- In the presence of DM, the risk of sudden cardiac death in both men and women is quadrupled.

- Both hyperglycaemia and hypoglycaemia are independently associated with increased risk of ventricular arrhythmias. Insulin-induced hypoglycaemia has been associated with nocturnal death (also called 'dead-in-bed syndrome') in T1DM, and arrhythmic deaths were reported in several T2DM trials. The mechanisms by which hyperglycaemia may produce ventricular instability may be increased sympathetic activity, increased cytosolic calcium content in myocytes, or both.

| Table 30-14: ESC Recommendations for the management of atrial fibrillation in patients with diabetes: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Screening: | | |
| <i>Opportunistic screening for AF by pulse taking or ECG is recommended in patients ≥ 65 years.</i> | I | B |
| <i>Opportunistic screening for AF by pulse taking or ECG is recommended in patients with diabetes < 65 years of age (particularly when other risk factors are present) because patients with diabetes exhibit a higher AF frequency at a younger age.</i> | I | C |
| <i>Systematic ECG screening should be considered to detect AF in patients aged ≥ 75 years, or those at high risk of stroke.</i> | IIa | B |
| Anticoagulation: | | |
| <i>Oral anticoagulation is recommended for preventing stroke in patients with AF and diabetes and with at least one additional (CHA₂DS₂-VASc) risk factor for stroke.</i> | I | A |
| <i>For preventing stroke in AF, NOACs are recommended in preference to VKAs, with the exception of patients with mechanical valve prostheses or moderate to severe mitral stenosis.</i> | I | A |
| <i>Oral anticoagulation should be considered for preventing stroke in patients with AF and diabetes but no other CHA₂DS₂-VASc risk factor for stroke. This includes patients with T1DM or T2DM < 65 years old.</i> | IIa | B |

Use of a formal, structured, bleeding risk score (HAS-BLED score) should be considered to identify modifiable and non-modifiable risk factors for bleeding in patients with diabetes and AF, and to identify patients in need of closer follow-up.

IIa

B

Chronic kidney disease (CKD) in diabetes:

CKD is defined as a reduction in eGFR to $< 60 \text{ mL/min/1.73m}^2$ and/or persistent proteinuria (e.g., urinary albumin: creatinine ratio $> 3 \text{ mg/mmol}$), sustained for > 3 months.

- CKD is associated with a high prevalence of CVD and should be considered in the highest risk group for risk factor management.
- Approximately 30% of patients with T1DM and 40% with T2DM will develop CKD.
- Albuminuria is an early marker of nephropathy and predicts both risk of kidney failure and CVD independently of eGFR.
- Increased risk of CAD accompanies CKD, often with calcification of atherosclerotic plaques. Accelerated vascular media calcification with increased vascular stiffness is also a feature of CKD and attributed to disordered calcium-phosphate metabolism, referred to as CKD-mineral bone disorder (CKD-MBD).
- Screening for kidney disease in patients with DM requires serum creatinine measurement to enable the calculation of eGFR and urine tests of albumin excretion.
- In CKD, HbA1c monitoring may be less reliable when eGFR is $< 30 \text{ mL/min/1.73 m}^2$, and self-monitoring or CGM may help safely achieve tight glycemic control in such patients.
- Optimizing glycemic and BP control may slow decline in kidney function.
- Several drugs developed to manage CVD risk or hyperglycemia have been shown to reduce the risk of CKD progression in large trials that recruited patients with T2DM and CKD. These include RAS inhibitors, SGLT2 inhibitors, and finerenone.
- Statins reduce the risk of major atherosclerotic events (i.e. coronary death, non-fatal MI, ischemic stroke, and coronary revascularization) in patients with CKD, but does not meaningfully slow progression of CKD. The goal in patients with CKD and diabetes should be to achieve the largest possible absolute reduction in LDL-C safely.

- In patients with T2DM and CKD, correcting renal anemia improves quality of life, but does not reduce the risk of CVD and may increase the risk of stroke. Renal specialist advice should be sought for managing a raised serum phosphate (> 1.5 mmol/L) or other evidence of CKD-MBD, and renal anemia (e.g. hemoglobin < 10 g/dL).

| Table 30-15: Chronic kidney disease classification by eGFR and albuminuria ⁽¹⁾ : | | | | |
|---|--|-------------------|-------------------|------------------------------|
| eGFR (mL/min/1.73 m ²) | Albuminuria categories (albumin:creatinine ratio spot urine) | | | |
| | A1 (< 3 mg/mmol) | A2 (3-30 mg/mmol) | A3 (> 30 mg/mmol) | |
| G1 (≥ 90) | No CKD | G1 A2 | G1 A3 | <i>Increasing risk ↓</i> |
| G2 (60-89) | No CKD | G2 A2 | G2 A3 | |
| G3a (45-59) | G3a A1 | G3a A2 | G3a A3 | |
| G3b (30-44) | G3b A1 | G3b A2 | G3b A3 | |
| G4 (15-29) | G4 A1 | G4 A2 | G4 A3 | |
| G5 (< 15) | G5 A1 | G5 A2 | G5 A3 | |
| | <i>Increasing risk →</i> | | | |

(1) **Green**= low risk; **Yellow**= medium risk; **Orange**= high risk; **Red**= very high risk.

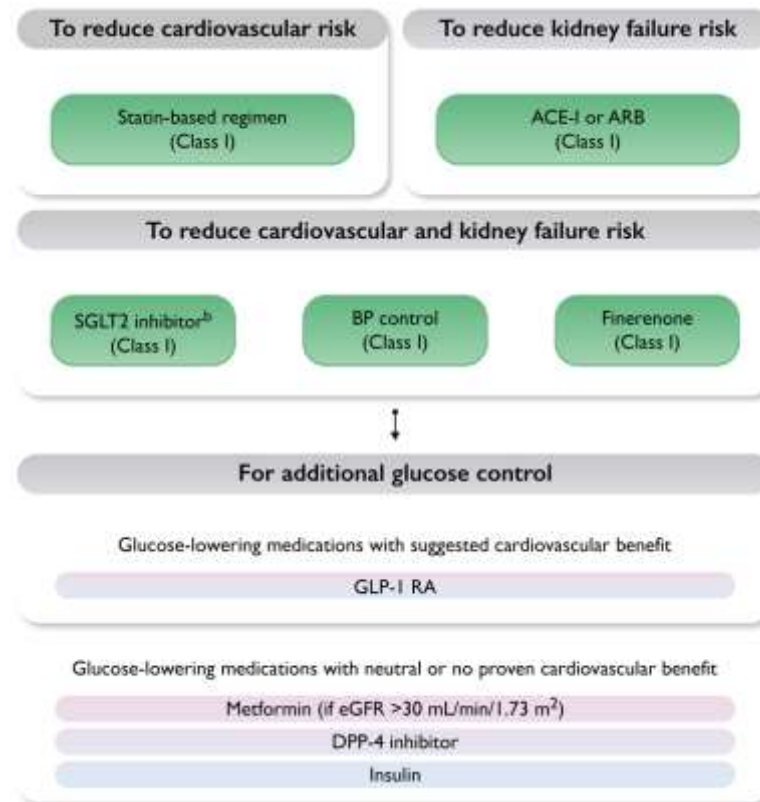


Figure 30-4: Pharmacological management to reduce cardiovascular or kidney failure risk in patients with type 2 diabetes and chronic kidney disease. UACR: urinary albumin-to-creatinine ratio. A) A statin-based regimen reduces CV risk in CKD while ACE-I or ARBs reduce kidney failure risk; SGLT2 inhibitors, BP control, and finerenone reduce both CV risk and kidney failure risk. SGLT2 inhibitors, RAS inhibitors, and finerenone are particularly effective at reducing risk of kidney failure when albuminuria is present [e.g. UACR ≥ 3 mg/mmol (30 mg/g); stage A2 and A3]. **B)** Canagliflozin, empagliflozin, or dapagliflozin. **Source:** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.

Table 30-16: ESC Recommendations for the prevention and management of chronic kidney disease in patients with diabetes:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Intensive LDL-C lowering with statins or a statin/ ezetimibe combination is recommended ⁽¹⁾.</i> | I | A |
| <i>A BP target of $\leq 130/80$ mmHg is recommended to reduce risk of CVD and albuminuria.</i> | I | A |
| <i>Personalized HbA1c targets 6.5–8.0% (48–64 mmol/ mol) are recommended, with a target $<7.0\%$ (<53 mmol/mol) to reduce microvascular complications, wherever possible.</i> | I | A |
| <i>The maximum tolerated dose of an ACE-I or ARB is recommended.</i> | I | A |
| <i>A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) ⁽²⁾ is recommended in patients with T2DM and CKD with an eGFR ≥ 20 mL/min/1.73 m² to reduce the risk of CVD and kidney failure.</i> | I | A |
| <i>Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/ min/1.73 m² with a UACR ≥ 30 mg/mmol (≥ 300 mg/ g), or eGFR 25–60 mL/min/1.73 m² and UACR ≥ 3 mg/mmol (≥ 30 mg/g) to reduce CV events and kidney failure.</i> | I | A |
| <i>A GLP-1 RA is recommended at eGFR >15 mL/min/ 1.73 m² to achieve adequate glycemic control, due to low risk of hypoglycemia and beneficial effects on weight, CV risk, and albuminuria.</i> | I | A |
| <i>Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.</i> | I | A |
| <i>It is recommended that patients with diabetes are routinely screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR.</i> | I | B |

(1) Little evidence of benefit in patients on dialysis.

(2) Sotagliflozin reduces CV risk but has not demonstrated a reduction in the risk of kidney failure.

| | | |
|---|------------|----------|
| <i>Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes ⁽¹⁾.</i> | I | B |
| <i>Kidney specialist advice may be considered for managing a raised serum phosphate, other evidence of CKD-MBD, and renal anemia.</i> | IIb | C |
| <i>Combined use of an ARB with an ACE-I is not recommended.</i> | III | B |

Aortic and peripheral arterial diseases:

- **Carotid artery disease:**

- Thromboembolism from a carotid artery stenosis is the mechanism underlying 10-15% of all strokes, so carotid artery disease must be rapidly ruled out in all patients presenting with TIA or stroke.
- In patients with DM without a history of cerebrovascular disease, there is no evidence that carotid screening improves outcomes and systematic screening is not recommended.
- Asymptomatic carotid disease is frequently treated conservatively, and the patient is followed-up with duplex ultrasound.
- The management of carotid artery disease is similar in DM and non-DM patients.
- Carotid revascularization should be considered in asymptomatic patients in the presence of one or more indicators of increased stroke risk (previous TIA/stroke, ipsilateral silent infarction, stenosis progression, or high-risk plaques), and if the estimated peri-operative stroke or death rate is < 3% and the patient's life expectancy is > 5 years.
- In symptomatic patients, carotid revascularization is indicated if the stenosis is > 70%, and should be considered if the stenosis is > 50%, assuming that the estimated peri-operative stroke or death rate is < 6%.

- **Diabetes and aortic aneurysm:**

(1) ISCHEMIA-CKD trial primary and key secondary outcomes were a composite of 'death or non-fatal MI' and 'death, non-fatal MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest', respectively.

- Current evidence shows a lower risk of developing aortic aneurysm in patients with diabetes compared with persons without diabetes. There are different mechanisms under discussion including effects on extracellular matrix volume, extracellular matrix glycation, the formation of advanced glycation end-products, inflammation, oxidative stress, and intraluminal thrombus biology. Moreover, some medications, such as metformin used to treat diabetes, seem to have protective effects on the development of abdominal aortic aneurysms.

- **Lower Extremity Artery Disease:**

- LEAD is a common complication of DM, with one-third of patients hospitalized for LEAD having DM.
- Prolonged DM duration, suboptimal glycemic control, the coexistence of other CV risk factors, and/or other end-organ damage (e.g., proteinuria) increase LEAD prevalence.
- At any stage of LEAD, the coexistence of DM is associated with poorer prognosis.
- For patients with a diabetic foot ulcer (diabetic foot disease), the risk of death at 5 years is 2.5 times higher than for patients with diabetes but no foot ulcer.
- Compared with patients without diabetes, those with diabetes develop LEAD at a younger age and have faster LEAD progression, with more patients having CLTI. In addition, patients with diabetes have occlusions of arteries below the knee more often than do patients without diabetes.
- Patients with DM are at higher risk of chronic limb threatening ischemia (CLTI) as the first clinical manifestation of LEAD ⁽¹⁾, supporting regular screening with ABI measurement for early diagnosis. An ABI ≤ 0.90 is diagnostic for LEAD, with 80% sensitivity and 95% specificity in all populations. However, the accuracy of ABI is lower in patients with diabetes. Measuring ABI can be difficult due to medial calcinosis (ABI > 1.40), in which case, other tests are useful for diagnosing LEAD, including Doppler waveform analysis of the ankle arteries, or the toe-brachial index (TBI), which may be helpful because medial calcinosis barely affects digital arteries. A TBI < 0.70 is diagnostic for LEAD.

(1) *In patients with diabetes, pain is often masked because of peripheral neuropathy with decreased pain sensitivity. Therefore, atherosclerosis is often advanced when diagnosed.*

- The management of, and indications for, different treatment strategies are similar in patients with LEAD with or without DM, although the options for revascularization may be poorer because of diffuse and distal lesions.
- Note that, according to US FDA requirements, the amputation risk with canagliflozin is described in the Warnings and Precautions section of the prescribing information based on the CANVAS study. However, this finding has not been repeated in the CREDENCE trial comparing canagliflozin with placebo in patients with T2DM and CKD, nor in CVOTs with other SGLT2 inhibitors.

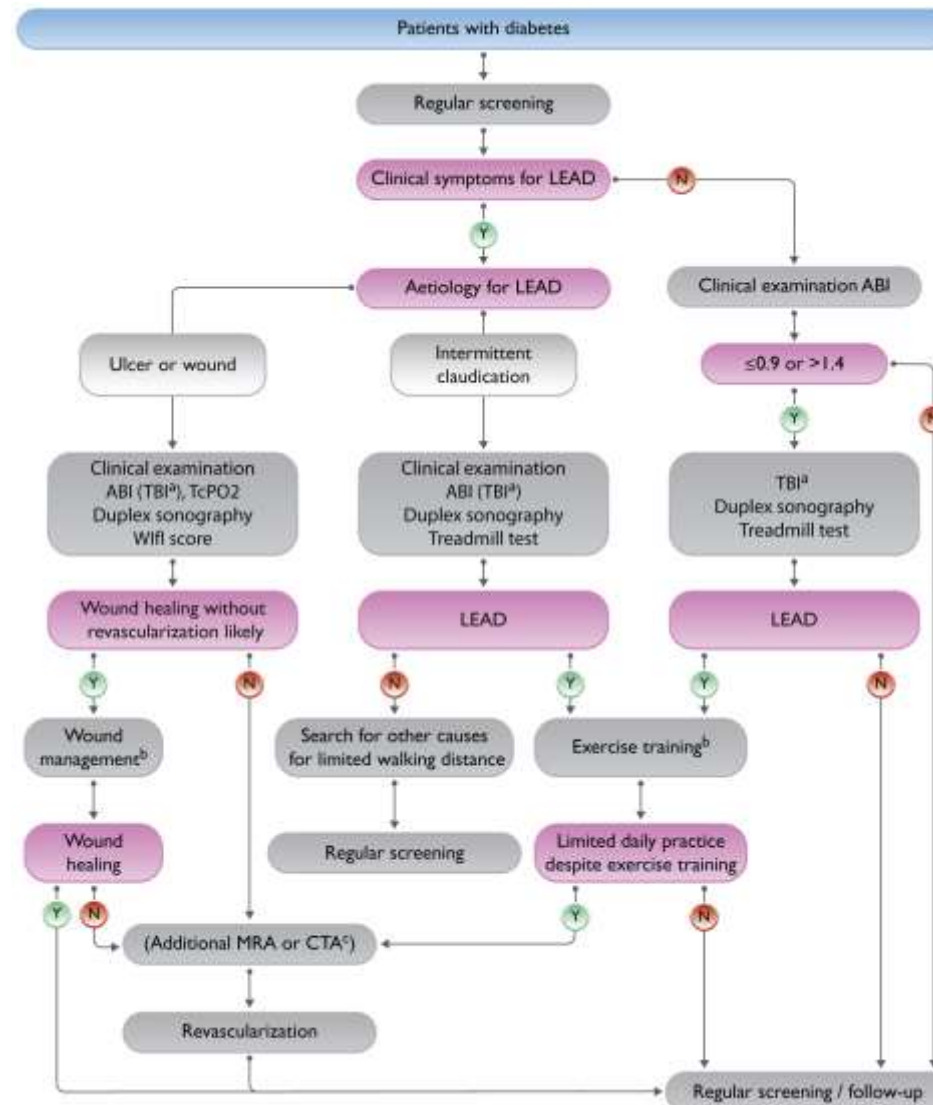


Figure 30-5: Screening for and managing lower-extremity artery disease in patients with diabetes. TBI, toe–brachial index; TcPO₂, transcutaneous oxygen pressure; Wifl, Wound, Ischemia, foot Infection. **A)** TBI when ABI >1.4. **C)** MRA or CTA when duplex sonography is not sufficient for planning revascularization. **Source:** 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes.

Table 30-17: ESC Recommendations for the management of peripheral arterial disease in patients with DM:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Carotid artery disease: | | |
| <i>In patients with diabetes and carotid artery disease, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.</i> | I | C |
| Aortic aneurysm: | | |
| <i>In patients with diabetes and aortic aneurysm, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.</i> | I | C |
| LEAD: | | |
| <i>In patients with diabetes and symptomatic LEAD, antiplatelet therapy is recommended.</i> | I | A |
| <i>In patients with diabetes and CLTI, it is recommended to assess the risk of amputation; the Wifl score is useful for this purpose.</i> | I | B |
| <i>As patients with diabetes and LEAD are at very high CV risk, a LDL-C target of <1.4 mmol/L (<55 mg/dL) and a LDL-C reduction of at least 50% is recommended.</i> | I | B |
| <i>Screening for LEAD is recommended on a regular basis, with clinical assessment and/or ABI measurement.</i> | I | C |
| <i>Patient education about foot care is recommended in patients with diabetes, and especially those with LEAD, even if asymptomatic. Early recognition of tissue loss and/or infection, and referral to a multidisciplinary team, is mandatory to improve limb salvage.</i> | I | C |

| | | |
|---|------------|----------|
| <i>An ABI ≤ 0.90 is diagnostic of LEAD, irrespective of symptoms. In symptomatic cases, further assessment including duplex ultrasound is recommended.</i> | I | C |
| <i>When ABI is elevated (>1.40), other non-invasive tests, including TBI or duplex ultrasound, are recommended.</i> | I | C |
| <i>Duplex ultrasound is recommended as the first-line imaging method to assess the anatomy and hemodynamic status of lower-extremity arteries.</i> | I | C |
| <i>In case of CLTI, revascularization is recommended whenever feasible for limb salvage.</i> | I | C |
| <i>In patients with chronic, symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and ASA (100 mg o.d.) should be considered.</i> | IIa | B |

Type 1 diabetes and cardiovascular disease

People with T1DM face a three-fold increase in mortality compared with the general population, which translates into an 11-year reduction in life expectancy; CVD mortality accounts for 30-44% of all deaths in patients with T1DM.

Reducing CV risk in patients with T1DM relates to both lowering HbA1c and controlling other classical CV risk factors, including BP and LDL-C. Therefore, glucose control target values are recommended for most adults with T1DM by the joint consensus report of the ADA and EASD: HbA1c $< 7.0\%$; pre-prandial glucose 80-130 mg/dL; and 1-2 h post-prandial glucose < 180 mg/dL. Hypoglycemia should be avoided.

- **CV risk assessment in type 1 diabetes:**

Determining ASCVD risk in patients with T1DM is less well studied than in patients with T2DM. Age at the onset and duration of diabetes are two risk factors that lead the estimation of CV risk. Thus, patients diagnosed with T1DM at an early age show an increased incidence of CVD. Several other risk factors related to diabetes management, include: glycemic control, insulin requirements, smoking, cardiac autonomic neuropathy, dysfunctional immune response, and insulin resistance.

- **Managing cardiovascular risk:**

- **Exercise and lifestyle:** Data on the effects of exercise on T1DM are inconclusive. Aerobic fitness improved HbA1c in patients with T1DM, but did not affect BMI, BP, and lipids.
- **Lipid lowering:** Statins remain the cornerstone of lipid-lowering treatment. In patients with T1DM at a younger age, starting statins early might be justified with long duration of disease, two additional risk factors, or microalbuminuria. Increased cholesterol absorption in T1DM compared with T2DM may explain why ezetimibe may reduce LDL-C more in T1DM than in T2DM.
- **Blood pressure:** People with T1DM may benefit from stringent BP-lowering strategies. Routine ambulatory BP monitoring is recommended to identify subjects with masked hypertension.
- **Antiplatelet therapy:** Antiplatelet agents may be beneficial in individuals with T1DM without symptomatic ASCVD who have at least one additional major CV risk factor.
- **Glucose-lowering agents beyond insulin:** GLP-1 RAs or SGLT2 inhibitors are currently not indicated for T1DM. For GLP-1 RAs, concerns have been raised about increased rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis. For SGLT2 inhibitors, adding at a lower than usual dose to insulin therapy in T1DM may reduce glucose variability and facilitate glucose control, thereby reducing insulin doses and hypoglycaemia. However, ketoacidosis at lower glucose levels, so called 'euglycaemic ketoacidosis', has been reported in 2–3% of patients (potentially lethal complication).
- **Renal protection in type 1 DM:** As in patients with T2DM, patients with T1DM should be regularly screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR. RAS blockade with an ACE-I prevents kidney failure in patients with T1DM and overt nephropathy.

Table 30-18: ESC Recommendations for patients with type 1 diabetes:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| <i>In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.</i> | I | C |

| | | |
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| <i>Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.</i> | I | C |
| <i>Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.</i> | IIa | B |
| <i>Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk $\geq 10\%$ to reduce CVD risk.</i> | IIa | B |
| <i>The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.</i> | IIb | B |

Important trials in the management of DM in CV diseases:

| Table 30-19: Clinical trials in cardiometabolism: | |
|---|--|
| Trial (date) | Summary |
| Effects of intensified glucose control: | |
| UKPDS (1999) | <p>Aim: To determine the effect of intensive glycemic control on the incidence of complications.</p> <p>Study: 4209 patients with newly diagnosed type 2 diabetes were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control. Although a clear reduction in microvascular complications was evident, the reduction in MI was marginal at 16%. In the study extension phase, the risk reduction in MI remained at 15%, which became significant as the number of cases increased.</p> |
| ACCORD (2008) | <p>Aim: To investigate whether intensive therapy to target normal HbA1C levels would reduce CV events in patients with type 2 DM who had either established CV disease or additional CV risk factors.</p> <p>Study: 10,251 patients with a median HbA1C of 8.1% were assigned to receive intensive therapy (targeting HbA1C < 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). The primary outcome was a composite of nonfatal MI, nonfatal stroke, or death from CV causes. As compared with standard therapy, the use of intensive therapy to target normal HbA1C levels for 3.5 years increased mortality and did not significantly reduce major CV events.</p> |
| ADVANCE (2008) | <p>Aim: To assess the effects on major vascular outcomes of lowering the HbA1C to a target of $\leq 6.5\%$ in patients with type 2 DM.</p> <p>Study: 11,140 patients with type 2 diabetes were randomly assigned to undergo either standard glucose control or intensive glucose control (defined as the use of gliclazide + other drugs as required to achieve a HbA1C $\leq 6.5\%$). Primary end points were composites of major macrovascular events (death from CV causes, nonfatal MI, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). A strategy</p> |

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| | <i>of intensive glucose control yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.</i> |
| VADT (2009) | <p>Aim: <i>To compare the effects of intensive and standard glucose control on CV events.</i></p> <p>Study: <i>1791 military veterans who had a suboptimal response to therapy for type 2 diabetes were randomly assigned to receive either intensive or standard glucose control. The primary outcome was the time from randomization to the first occurrence of a major CV event, a composite of MI, stroke, death from CV causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria (P = 0.01).</i></p> |
| DIGAMI 1 (2014) | <p>Aim: <i>To evaluate whether rapid metabolic control in diabetic patients with insulin-glucose infusion decreases mortality and morbidity.</i></p> <p>Study: <i>620 Patients with suspected MI in preceding 24 hours and blood glucose > 11 mM on admission (with or without prior diagnosis of diabetes) were randomized to continuous intravenous insulin infusion for 24 hours (started at 5 U/h) or until normoglycemia was achieved (goal of 7-10 mM), followed by subcutaneous insulin for 3 months versus conventional therapy. The primary endpoints was all-cause mortality. Insulin-glucose infusion followed by a multidose insulin therapy improved long-term survival in diabetic patients after AMI. Possible mechanisms for this benefit are that intense insulin may restore impaired platelet function, decrease PAI-1 activity, and improve metabolism of noninfarcted areas.</i></p> |
| DIGAMI 2 (2005) | <p>Aim: <i>To assess the possible benefits of an insulin-based management of diabetic patients with MI.</i></p> <p>Study: <i>1253 patients with type 2 diabetes and suspected acute MI randomly assigned to groups 1 (acute insulin-glucose infusion followed by insulin-based long-term glucose control), group 2 (insulin-glucose infusion followed by standard glucose control), and group 3 (routine metabolic management according to local practice). The primary endpoint was all-cause mortality. Acutely introduced, long-term insulin treatment did not improve</i></p> |

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| | <i>survival in type 2 diabetic patients following MI. However, an epidemiological analysis confirms that the glucose level is a strong, independent predictor of long-term mortality in this patient category.</i> |
| DCCT (1993) | <p>Aim: <i>To examine whether intensive glucose control could decrease the frequency and severity of long-term microvascular and neurologic complications in patients with type 1 DM.</i></p> <p>Study: <i>1441 patients with IDDM: 726 with no retinopathy at baseline (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in IDDM.</i></p> |
| EDIC (2005) | <p>Aim: <i>To determine the long-term effects of the original DCCT interventions on diabetic complications.</i></p> <p>Study: <i>The EDIC study enrolled patients who had previously participated in the DCCT study. The primary outcome measure for the EDIC study was the time to the first of any CV disease event. EDIC study has found that intensive diabetes therapy had long-term beneficial effects on the risk of CV disease in patients with type 1 diabetes and that the differences in outcomes between the intensive and conventional therapy groups persist after long-term study.</i></p> |
| Antithrombotic in DM: | |
| ASCEND (2018) | <p>Aim: <i>To assess the efficacy and safety of enteric-coated aspirin at a dose of 100 mg daily in persons who had DM without manifest CV disease.</i></p> <p>Study: <i>15,480 adults who had diabetes but no evident cardiovascular disease were randomly assigned to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). Aspirin use prevented serious vascular events in persons who</i></p> |

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| | <i>had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.</i> |
| ARRIVE (2018) | <p>Aim: To evaluate aspirin among patients with moderate risk of CV disease (10-year risk of coronary heart disease 10-20%).</p> <p>Study: 12546 patients at moderate risk of coronary heart disease were randomized to aspirin 100 mg daily versus placebo. The primary efficacy outcome, cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. Among patients at moderate risk of coronary heart disease, the use of aspirin was not beneficial. Aspirin was not associated with a reduction in adverse cardiovascular events. Bleeding events were low and similar between treatment arms.</p> |
| Lifestyle modification: | |
| Look AHEAD (2013) | <p>Aim: To assess whether weight loss through caloric restriction and increased physical activity decrease CV morbidity and mortality among overweight or obese adults with type 2 DM.</p> <p>Study: 5145 overweight or obese patients with type 2 DM were randomly assigned to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The primary outcome was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years. An intensive lifestyle intervention focusing on weight loss did not reduce the rate of CV events in overweight or obese adults with type 2 DM.</p> |
| DiRECT (2017) | <p>Aim: To assess whether intensive weight management within routine primary care would achieve remission of type 2 DM.</p> <p>Study: 306 participants were aged 20-65 years, with type 2 DM duration of < 6 years and BMI 27-45 kg/m², and were not receiving insulin. Weight loss was initiated by total diet replacement, and weight loss maintenance support was provided for 2 years. Remissions (HbA_{1c} < 6.5%, without antidiabetes medications) in the intervention group were achieved by 46% of participants at 12 months and by 53/149 participants (36%) at 24</p> |

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| | <i>months. at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care.</i> |
| SOS (2007) | <p>Aim: <i>To evaluate whether bariatric surgery is associated with lower mortality, as compared with conventional treatment.</i></p> <p>Study: <i>2010 obese subjects who underwent bariatric surgery [gastric bypass (13%), banding (19%) and vertical banded gastroplasty (68%)] and 2037 contemporaneously matched obese control subjects receiving usual care. Overall mortality is reported during an average of 10.9 years of follow-up. Bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality.</i></p> |
| CORDIOPREV (2022) | <p>Aim: <i>To compare the effects of Mediterranean diet and a low-fat diet in secondary prevention of CV disease.</i></p> <p>Study: <i>1002 patients with established coronary heart disease (aged 20–75 years) were randomly assigned to receive a Mediterranean diet or a low-fat diet intervention, with a follow-up of 7 years. The primary outcome (assessed by intention to treat) was a composite of MACE including MI, revascularisation, ischaemic stroke, peripheral artery disease, and CV death. The Mediterranean diet was superior to the low-fat diet in preventing MACE in secondary prevention.</i></p> |
| CV effects of glucose-lowering drugs: | |
| Sulfonylureas: | |
| CAROLINA (2019) | <p>Aim: <i>To assess the effect of linagliptin compared with glimepiride on MACE in patients with relatively early type 2 DM and CV risk.</i></p> <p>Study: <i>6042 participants with type 2 DM with HbA1C of 6.5-8.5%, and elevated CV risk (documented atherosclerotic CV disease, multiple CV risk factors, aged ≥ 70 years, and evidence of microvascular complications) were randomized to receive linagliptin (5 mg once daily) <u>or</u> glimepiride (1 to 4 mg once daily) in addition to usual care. The use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite CV outcome.</i></p> |
| Thiazolidinediones: | |

| | |
|---|---|
| PROactive (2005) | <p>Aim: To ascertain whether pioglitazone reduces macrovascular morbidity and mortality in high-risk patients with type 2 DM.</p> <p>Study: 5238 patients with type 2 DM who had evidence of macrovascular disease were assigned to pioglitazone (titrated from 15 mg to 45 mg) or placebo, to be taken in addition to their glucose-lowering drugs. The primary endpoint was the composite of all-cause mortality, non fatal MI, stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Pioglitazone reduces the composite of all-cause mortality, non-fatal MI, and stroke in patients with type 2 DM who have a high risk of macrovascular events.</p> |
| IRIS (2016) | <p>Aim: To assess if pioglitazone would reduce the rates of stroke and MI after stroke/TIA in patients without diabetes who have insulin resistance.</p> <p>Study: 3876 patients who had had a recent ischemic stroke or TIA were randomly assigned to receive either pioglitazone (target dose, 45 mg daily) or placebo. The primary outcome was fatal or nonfatal stroke or MI. Pioglitazone was associated with a lower risk of stroke, MI or DM but with higher risks of weight gain, edema, and fracture.</p> |
| Dipeptidyl peptidase-4 inhibitors: | |
| SAVOR-TIMI 53 (2013) | <p>Aim: To evaluate the safety and efficacy of saxagliptin on CV outcomes in patients with DM who are at risk for CV events.</p> <p>Study: 16,492 patients with type 2 diabetes who had a history of, or were at risk for, CV events were randomly assigned to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of CV death, MI, or ischemic stroke. DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce CV risk in patients with diabetes.</p> |

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| EXAMINE (013) | <p>Aim: To assess CV outcomes with alogliptin compared with placebo in patients with type 2 DM who had had a recent ACS.</p> <p>Study: 5380 patients with type 2 diabetes and recent ACS requiring hospitalization within the previous 15 to 90 days were randomly assigned to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from CV causes, nonfatal MI, or nonfatal stroke. the rates of MACE were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.</p> |
| TECOS (2015) | <p>Aim: To assess the long-term CV safety of adding sitagliptin in patients with type 2 DM and established CV disease.</p> <p>Study: 14,671 patients with type 2 DM and established CV disease were assigned to add either sitagliptin or placebo to their existing therapy. The primary outcome was composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. In patients with type 2 DM and established CV disease, adding sitagliptin to usual care did not appear to increase the risk of MACE, HF hospitalization, or other adverse events.</p> |
| CARMELINA (2019) | <p>Aim: To assess the effect of linagliptin compared with placebo on risk of major cardiovascular (CV) events in type 2 diabetes at high CV risk</p> <p>Study: 6979 adults with type 2 diabetes, hemoglobin A_{1c} of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria) were randomized to receive linagliptin, 5 mg once daily, or placebo once daily added to usual care. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines. Participants with ESRD were excluded. Among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.</p> |

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|---|--|
| CAROLINA (2019) | <p>Aim: To assess the effect of linagliptin compared with glimepiride on MACE in patients with relatively early type 2 DM and elevated CV risk</p> <p>Study: 6042 participants with type 2 diabetes, HbA1c of 6.5% to 8.5%, and elevated cardiovascular risk were eligible for inclusion. were randomized to receive 5 mg of linagliptin once daily or 1 to 4 mg of glimepiride once daily in addition to usual care. Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.</p> |
| Glucagon-like peptide-1 receptor agonists: | |
| ELIXA (2015) | <p>Aim: To assess the effects of lixisenatide on CV outcomes in patients with type 2 DM who had had a recent ACS.</p> <p>Study: 6068 patients with type 2 diabetes who had had a recent ACS within the previous 180 days were randomly assigned to receive lixisenatide or placebo in addition to locally determined standards of care. the primary composite end point of CV death, MI, stroke, or hospitalization for unstable angina. The addition of lixisenatide to usual care did not significantly alter the rate of MACE or other serious adverse events.</p> |
| LEADER (2016) | <p>Aim: To assess the CV safety of liraglutide in patients with type 2 DM at high risk for CV events.</p> <p>Study: 9340 patients with type 2 diabetes and high CV risk were randomly assigned to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. In the time-to-event analysis, the primary composite outcome was lower with liraglutide than with placebo.</p> |
| SUSTAIN-6 (2016) | <p>Aim: To assess the noninferiority of semaglutide as compared with placebo in terms of CV safety in patients with type 2 DM.</p> <p>Study: 3297 patients with type 2 diabetes who were on a standard-care regimen were randomly assigned to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The rate of CV death, nonfatal MI, or</p> |

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| | <i>nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide.</i> |
| EXSCEL (2017) | <p>Aim: <i>To assess the CV effects of exenatide to usual care in patients with type 2 diabetes.</i></p> <p>Study: <i>14752 patients with type 2 diabetes, with or without previous cardiovascular disease, were randomly assigned to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly. The primary composite outcome was the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. Among patients with type 2 diabetes with or without previous CV disease, the incidence of MACE did not differ significantly between patients who received exenatide and those who received placebo.</i></p> |
| PIONEER 6 (2019) | <p>Aim: <i>To investigate the CV safety of oral semaglutide in subjects with type 2 diabetes.</i></p> <p>Study: <i>3183 patients at high cardiovascular risk (age of ≥ 50 years with established CV or CKD, or age of ≥ 60 years with CV risk factors only) were randomly assigned to receive oral semaglutide or placebo. The primary outcome in a time-to-event analysis was the first occurrence of a major adverse CV event (death from CV causes, nonfatal MI, or nonfatal stroke). The trial was designed to rule out 80% excess CV risk as compared with placebo. The CV risk profile of oral semaglutide was not inferior to that of placebo.</i></p> |
| Harmony Outcomes (2018) | <p>Aim: <i>To assess the CV safety of albiglutide in patients with type 2 diabetes at high risk for CV events.</i></p> <p>Study: <i>9,463 patients aged ≥ 40 years with T2DM, prior atherosclerotic CV disease, and suboptimal glycemic control were assigned to albiglutide 30 mg (potentially increasing to 50 mg) or matching placebo administered once weekly by subcutaneous injection. Albiglutide was superior to placebo with respect to MACE. Evidence-based GLP-1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of CV events in patients with type 2 diabetes.</i></p> |
| REWIND (2019) | <p>Aim: <i>To assess the effect of the dulaglutide on MACE when added to the existing antihyperglycaemic regimens of individuals with type 2 DM.</i></p> <p>Study: <i>9901 participants aged ≥ 50 years with type 2 diabetes who had either a previous CV event or CV risk factors were randomly assigned to dulaglutide or placebo. The primary outcome was the first occurrence of the</i></p> |

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| | <i>composite endpoint of non-fatal MI, non-fatal stroke, or death from CV causes. Dulaglutide is superior to placebo in improving glycemic control and reducing CV events in patients with type 2 DM and higher CV risk.</i> |
| Sodium-glucose co-transporter 2 inhibitors: | |
| EMPA-REG OUTCOME (2015) | <p>Aim: <i>To assess the CV safety of empagliflozin in patients with type 2 diabetes mellitus at high risk for CV events.</i></p> <p>Study: <i>7020 patients with type 2 diabetes at high CV risk were randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from CV causes, nonfatal MI, or nonfatal stroke. Patients who received empagliflozin, as compared with placebo, had a lower rate of the primary composite CV outcome and of death from any cause when added to standard care.</i></p> |
| CANVAS (2017) | <p>Aim: <i>To evaluate the canagliflozin compared with placebo among patients with type 2 diabetes.</i></p> <p>Study: <i>10,142 participants with type 2 diabetes and high cardiovascular risk were randomly assigned to receive canagliflozin or placebo. The primary outcome was a composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. Patients treated with canagliflozin had a lower risk of CV events, but a greater risk of amputation, primarily at the level of the toe or metatarsal.</i></p> |
| DECLARE-TIMI 58 (2019) | <p>Aim: <i>To evaluate the effects of dapagliflozin on CV and renal outcomes in patients who had or were at risk for atherosclerotic CV disease.</i></p> <p>Study: <i>17,160 patients with type 2 diabetes who had or were at risk for atherosclerotic CV disease were randomly assigned to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse CV events (MACE), defined as CV death, MI, or ischemic stroke. Dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of CV death or HF hospitalization.</i></p> |
| VERTIS CV (2020) | <p>Aim: <i>To assess the long-term effects of ertugliflozin on cardiovascular and renal outcomes.</i></p> <p>Study: <i>8246 patients with type 2 DM and ASCVD were randomly assigned to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. The primary outcome was MACE. Among patients with type 2 diabetes and ASCVD, ertugliflozin was noninferior to placebo with respect to MACE.</i></p> |
| Insulin: | |

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| ORIGIN (2012) | <p>Aim: To assess whether provision sufficient basal insulin to normalize fasting plasma glucose levels may reduce CV events.</p> <p>Study: 12,537 people with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 DM were randomly assigned to receive insulin glargine (with a target fasting blood glucose level of ≤ 95 mg/dl or standard care and to receive n-3 fatty acids or placebo with the use of a 2-by-2 factorial design. The results of the comparison between insulin glargine and standard care are reported here. The coprimary outcomes were nonfatal MI, nonfatal stroke, or death from CV causes and these events plus revascularization or HF hospitalization. When used to target normal fasting plasma glucose levels for more than 6 years, insulin glargine had a neutral effect on CV outcomes and cancers. Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight.</p> |
| DEVOTE (2017) | <p>Aim: To assess the cardiovascular safety of degludec, as compared with glargine.</p> <p>Study: 7637 patients with type 2 diabetes were randomly assigned to receive either insulin degludec or insulin glargine U100 once daily between dinner and bedtime in a double-blind, treat-to-target, event-driven cardiovascular outcomes trial. The primary composite outcome in the time-to-event analysis was the first occurrence of an adjudicated MACE (death from cardiovascular causes, nonfatal MI, or nonfatal stroke. Among patients with type 2 DM at high risk for CV events, degludec was noninferior to glargine with respect to the incidence of MACE.</p> |
| DM and CKD: | |
| FIDELIO-DKD (2020) | <p>Aim: To assess whether finerenone slows CKD progression and reduces CV morbidity and mortality in advanced CKD and type 2 diabetes.</p> <p>Study: 5734 patients with CKD and type 2 diabetes were randomly assigned to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio of 30-300, eGFR 25-60 ml/min/1.73 m², and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300-5000 and eGFR of 25-75 ml/min/1.73 m². The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease</p> |

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| | <i>of at least 40% in the eGFR from baseline, or death from renal causes. In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.</i> |
| FIGARO-DKD (2021) | <p>Aim: <i>To evaluate whether finerenone would lead to lower risks of CV events and CV mortality among patients with either stage 2 to 4 CKD and moderately elevated albuminuria <u>or</u> stage 1 or 2 CKD and severely increased albuminuria.</i></p> <p>Study: <i>7437 patients with CKD and type 2 diabetes were randomly assigned to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio of 30-300, eGFR 25-90 ml/min/1.73 m² (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300-5000 and an eGFR ≥ 60 ml/min/1.73 m² (stage 1 or 2 CKD). The primary outcome was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or HF hospitalization. Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone improved CV outcomes as compared with placebo.</i></p> |
| CREDESCENCE (2019) | <p>Aim: <i>To assess the effect of canagliflozin on renal outcomes among patients with type 2 DM and CKD.</i></p> <p>Study: <i>4401 patients with type 2 diabetes and albuminuric CKD were randomly assigned to receive canagliflozin (100 mg daily) or placebo. All the patients had an eGFR of 30-90 ml/min/1.73 m² and albuminuria and were treated with RAS blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of < 15 ml/min/1.73 m²), a doubling of the serum creatinine level, or death from renal or CV causes. The risk of kidney failure and CV events was lower in the canagliflozin group at a median follow-up of 2.62 years.</i></p> |
| DAPA-CKD (2020) | <p>Aim: <i>To assess the effect of dapagliflozin in patients with CKD, with or without type 2 DM.</i></p> <p>Study: <i>4304 participants with an eGFR of 25 to 75 ml/min/1.73 m² and a urinary albumin-to-creatinine ratio of 200 to 5000 were randomly assigned to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Among patients with CKD, regardless of the presence or absence of DM, the risk</i></p> |

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| | <i>of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.</i> |
| SCORED (2021) | <p>Aim: <i>To assess the efficacy and safety of sotagliflozin in preventing CV events in patients with DM with CKD with or without albuminuria.</i></p> <p>Study: <i>10584 patients with type 2 DM (HbA1c $\geq 7\%$), chronic kidney disease (eGFR, 25-60 ml/min/1.73 m²), and risks for cardiovascular disease were randomly assigned in a 1:1 ratio to receive sotagliflozin or placebo. The primary end point was the composite of the total number of deaths from CV causes, HF hospitalizations, and urgent visits for HF. In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse event (Diarrhea, genital mycotic infections, volume depletion, and DKA).</i></p> |
| EMPA-KIDNEY (2023) | <p>Aim: <i>To assess the effects of empagliflozin in patients with CKD who are at risk for disease progression.</i></p> <p>Study: <i>6609 patients with CKD who had an eGFR of 20-45 ml/min/1.73 m², or who had an eGFR of 45-90 ml/min/1.73 m² with a urinary albumin-to-creatinine ratio of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of CV mortality or progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to < 10 ml/min/1.73 m², a sustained decrease in eGFR of $\geq 40\%$ from baseline, or death from renal causes). Among a wide range of patients with CKD who were at risk for disease progression, empagliflozin led to a lower risk of progression of kidney disease or death from CV causes than placebo.</i></p> |

References and suggested readings:

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Section

X

Management of Cardiovascular Diseases in Specific Circumstances

TO THE POINT

Chapter 31:

Cardiovascular management in non-cardiac surgery

Clinical risk evaluation:

Cardiovascular morbidity and mortality in patients undergoing non-cardiac surgery (NCS) are determined by two main factors: patient-related risk and type of surgery or procedure, including the circumstances under which it takes place (experience of institution, elective vs. emergency procedure). The risk may be reduced by an adequate pre-operative evaluation and proper selection of type and timing of the surgical procedure.

• Surgery-related risk:

The surgical risk estimate is a broad approximation of 30-day risk of CV death, MI, and stroke, which only takes into account the specific surgical intervention without considering the patient's comorbidities.

Table 31-1: Surgical risk estimate according to type of surgery or intervention:

| Low surgical risk (< 1%) | Intermediate surgical risk (1-5%) | High surgical risk (> 5%) |
|--|---|--|
| <ul style="list-style-type: none">○Breast○Dental○Endocrine: thyroid○Eye○Gynecological: minor○Orthopedic: minor○Reconstructive○Superficial surgery | <ul style="list-style-type: none">○Carotid asymptomatic (CEA or CAS)○Carotid symptomatic (CEA)○Endovascular aortic aneurysm repair○Head or neck surgery○Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy○Intrathoracic: non-major | <ul style="list-style-type: none">○Adrenal resection○Aortic and major vascular surgery○Carotid symptomatic (CAS)○Duodenal-pancreatic surgery○Liver resection, bile duct surgery○Oesophagectomy○Open lower limb revascularization for acute limb ischemia or amputation |

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| <ul style="list-style-type: none"> ○ <i>Urological: minor</i> ○ <i>VATS minor lung resection</i> | <ul style="list-style-type: none"> ○ <i>Neurological or orthopedic: major (hip and spine surgery)</i> ○ <i>Peripheral arterial angioplasty</i> ○ <i>Renal transplants</i> ○ <i>Urological or gynecological: major</i> | <ul style="list-style-type: none"> ○ <i>Pneumonectomy</i> ○ <i>Pulmonary or liver transplant</i> ○ <i>Repair of perforated bowel</i> ○ <i>Total cystectomy</i> |
|--|---|--|

- **Patient-related risk:**

Patient-related risk is determined by patient's age, the CV risk factors (e.g., smoking, hypertension, DM, dyslipidemia, family disposition) or established CV disease, and comorbidities. Patients aged < 65 years without signs, symptoms, or history of CVD or CV risk factors are considered to be of low risk, while patients with established CVD are considered to be at high risk of CV complications.

- **Initial assessment:**

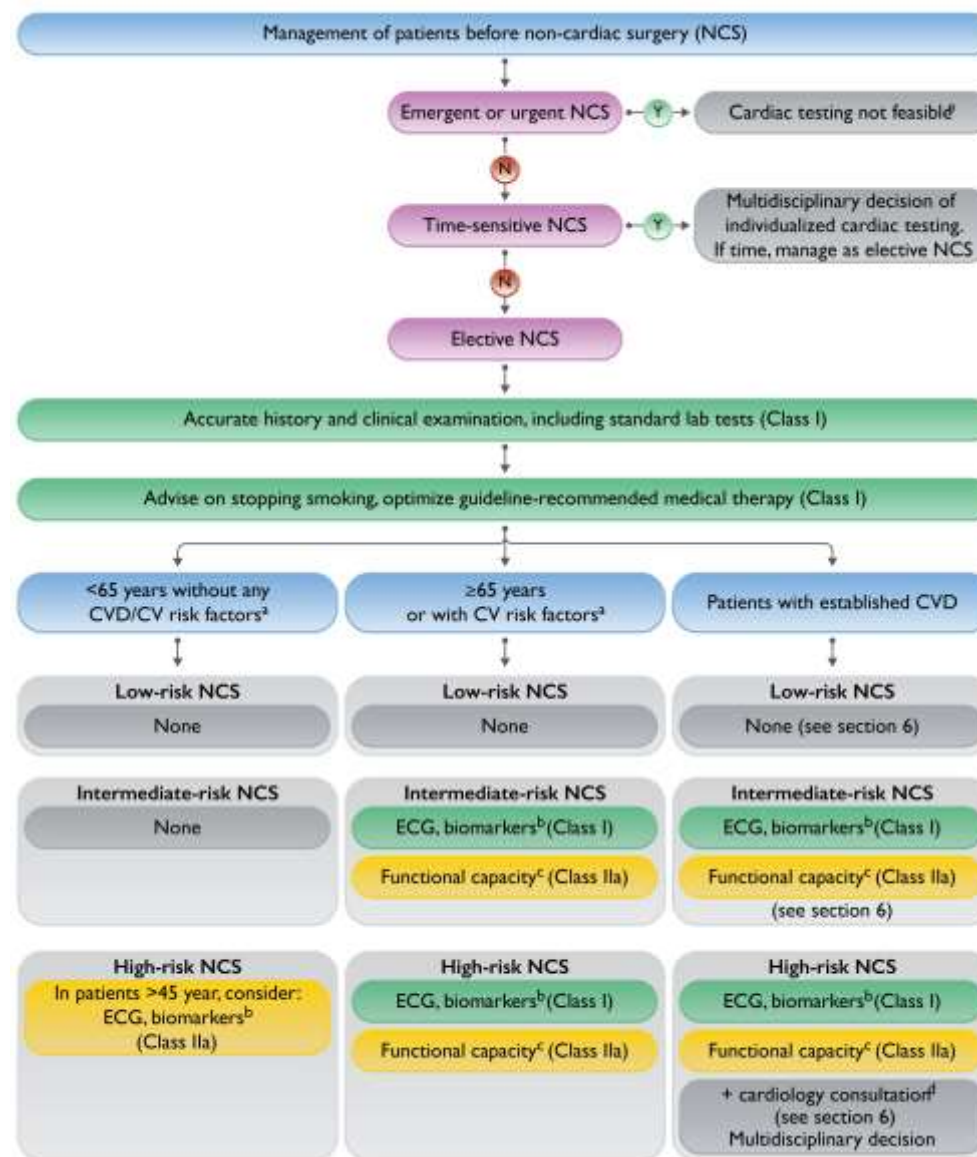


Figure 31-1: Pre-operative assessment before non-cardiac surgery. (A) CV risk factors: hypertension, smoking, dyslipidaemia, diabetes, family history of CVD. **(B)** Biomarkers: hs-cTn T/I (Class I) and/or BNP/NT-proBNP (Class IIa). If pathological, consult a cardiologist. **(C)** Functional capacity based on Duke Activity Status Index (DASI) or the ability to climb two flights of stairs. **(E)** Close follow-up after intervention and subsequent management of heart disease are advised. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

| Table 31-2: ESC Recommendations for patients scheduled for non-cardiac surgery: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| All patients: | | |
| <i>In all patients scheduled for NCS, an accurate history and clinical examination are recommended.</i> | I | C |
| <i>It is recommended to perform a pre-operative risk assessment, ideally at the same time as the NCS is proposed.</i> | I | B |
| <i>If time allows, it is recommended to optimize guideline-recommended treatment of CVD and CV risk factors before NCS.</i> | I | C |
| Patients aged < 65 years without cardiovascular disease: | | |
| <i>In patients with a family history of genetic cardiomyopathy, it is recommended to perform an ECG and TTE before NCS, regardless of age and symptoms.</i> | I | C |
| <i>In patients aged 45-65 years without signs, symptoms, or history of CVD, ECG and biomarkers should be considered before high-risk NCS.</i> | IIa | C |

• **Patients with murmurs, chest pain, dyspnea, or peripheral oedema:**

Patients without known CVD and scheduled for elective or acute NCS are often referred to a cardiologist because of symptoms or signs that may be caused by CVD. Murmurs, chest pain, dyspnea, and oedema may suggest severe CVD, but may also be caused by non-cardiac disease. Thus, the medical history, family history, and risk factors have to be obtained and considered. The patient's physical capacity should be assessed. The need for further evaluation of the patient should be decided according to the risk of the planned surgery.

| Table 31-3: ESC Recommendations for pre-operative assessment in patients with previously unknown murmur, angina, dyspnea, or peripheral oedema: | | |
|---|-------|-------|
| Recommendations | Class | Level |

| | | |
|--|-----|---|
| Newly detected murmur: | | |
| <i>In patients with a newly detected murmur and symptoms or signs of CVD, TTE is recommended before NCS.</i> | I | C |
| <i>In patients with a newly detected murmur suggesting clinically significant pathology, TTE is recommended before high-risk NCS.</i> | I | C |
| <i>In patients with a newly detected murmur, but without other signs or symptoms of CVD, TTE should be considered before moderate-risk NCS.</i> | IIa | C |
| Previously unknown angina: | | |
| <i>If a patient scheduled for elective NCS has chest pain or other symptoms suggestive of undetected CAD, further diagnostic work-up before NCS is recommended.</i> | I | C |
| <i>If a patient in need of acute NCS also has chest pain or other symptoms suggestive of undetected CAD, a multidisciplinary assessment approach is recommended to choose the treatment with lowest total risk for the patient.</i> | I | C |
| Dyspnea and/or peripheral oedema: | | |
| <i>In patients with dyspnea and/or peripheral oedema, an ECG and an NT-proBNP/BNP test is indicated before NCS, unless there is a certain non-cardiac explanation.</i> | I | C |
| <i>In patients with dyspnea and/or peripheral oedema and elevated NT-proBNP/BNP, TTE is recommended before NCS ⁽¹⁾.</i> | I | C |

(1) If BNP/NT-proBNP testing is unavailable, TTE should be considered.

Pre-operative assessment tools:

Several risk indices have been developed based on multivariable analyses of observational data and have been validated during the last decade. Most risk calculators integrate both patient-related and surgery-related risk factors, but none of them include biomarkers among their variables. ESC guidelines don't recommend one specific risk score.

Table 31-4: ESC Recommendations for pre-operative risk assessment:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Frailty and functional capacity: | | |
| <i>In patients aged ≥ 70 years and scheduled to undergo intermediate- or high-risk NCS, frailty screening should be considered using a validated screening tool.</i> | IIa | B |
| <i>Adjusting risk assessments according to self-reported ability to climb two flights of stairs (Equivalent to 4 METs) should be considered in patients referred for intermediate- or high-risk NCS.</i> | IIa | B |
| ECG: | | |
| <i>In patients who have known CVD or CV risk factors (including age ≥ 65 years), or symptoms or signs suggestive of CVD it is recommended to obtain a pre-operative 12-lead ECG before intermediate- and high-risk NCS.</i> | I | C |
| Biomarkers: | | |
| <i>In patients who have known CVD, CV risk factors (including age ≥ 65 years), or symptoms suggestive of CVD, who will undergo intermediate- and high-risk NCS, - it is recommended to measure hs-cTn T or I before, and at 24 h and 48 h afterwards ⁽¹⁾.</i> | I | B |
| | IIa | B |

(1) Abnormal pre-operative hs-cTn T/I: more than ULN.

| | | |
|--|-----|---|
| - it should be considered to measure BNP or NT-proBNP ⁽¹⁾ . | | |
| In low-risk patients undergoing low- and intermediate-risk NCS, it is not recommended to routinely obtain pre-operative ECG, hs-cTn T/I, or BNP/NT-proBNP concentrations. | III | B |
| Transthoracic echocardiography ⁽²⁾: | | |
| TTE is recommended in patients with poor functional capacity and/or high NT-proBNP/BNP, <u>or</u> if murmurs are detected before high-risk NCS, in order to undertake risk reduction strategies. | I | B |
| TTE should be considered in patients with suspected new CVD <u>or</u> unexplained signs or symptoms before high-risk NCS. | IIa | B |
| TTE may be considered in patients with poor functional capacity, abnormal ECG, high NT proBNP/BNP (≥ 125 pg/mL and 35 pg/mL), or ≥ 1 clinical risk factor before intermediate-risk NCS. | IIb | B |
| To avoid delaying surgery, a FOCUS exam performed by trained specialists may be considered as an alternative to TTE for pre-operative triage. | IIb | B |
| Routine pre-operative evaluation of LV function is not recommended. | III | C |
| Stress imaging ⁽³⁾: | | |

(1) Abnormal BNP: ≥ 35 pg/mL; abnormal NT-proBNP: ≥ 125 pg/mL.

(2) In large retrospective cohorts, routine pre-operative TTE before high-risk NCS did not reduce the risk of post-operative MACE or provide more information than clinical risk models.

(3) A high-risk stress test result (stress echo or nuclear stress test) is associated with a 10-25% risk of perioperative death or MI, while a normal stress test result is associated with a 0-4% risk of death or MI.

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| <i>Stress imaging is recommended before high-risk elective NCS in patients with poor functional capacity ⁽¹⁾ and high likelihood of CAD ⁽²⁾ or high clinical risk ⁽³⁾.</i> | I | B |
| <i>Stress imaging should be considered before high-risk NCS in asymptomatic patients with poor functional capacity, and previous PCI or CABG.</i> | IIa | C |
| <i>Stress imaging may be considered before intermediate-risk NCS when ischemia is of concern in patients with clinical risk factors and poor functional capacity.</i> | IIb | B |
| <i>Stress imaging is not recommended routinely before NCS.</i> | III | C |
| Coronary angiography: | | |
| <i>It is recommended to use the same indications for ICA and revascularization pre-operatively as in the non-surgical setting.</i> | I | C |
| <i>CCTA should be considered to rule out CAD in patients with suspected CCS <u>or</u> biomarker-negative NSTEMI-ACS in case of low-to-intermediate clinical likelihood of CAD, <u>or</u> in patients unsuitable for non-invasive functional testing undergoing non-urgent, intermediate-, and high-risk NCS.</i> | IIa | C |
| <i>Pre-operative ICA may be considered in stable CCS patients undergoing elective surgical CEA.</i> | IIb | B |
| <i>Routine pre-operative ICA is not recommended in stable CCS patients undergoing low- or intermediate-risk NCS.</i> | III | C |

(1) Physical capacity based on Duke Activity Status Index (DASI) **or** inability to climb two flights of stairs.

(2) Pre-test probability > 15% based on age, sex, and nature of symptoms, **or** two or more risk factors for CVD (dyslipidemia, diabetes, hypertension, smoking, family history of CVD), **or** resting ECG changes (Q wave or ST-segment/T wave changes), **or** LV dysfunction suggestive of CAD.

(3) One or more clinical risk factors according to the Revised Cardiac Risk Index or Lee index (ischemic heart disease, cerebrovascular disease, history of congestive HF, serum Cr. > 2 mg/dL, DM requiring insulin therapy).

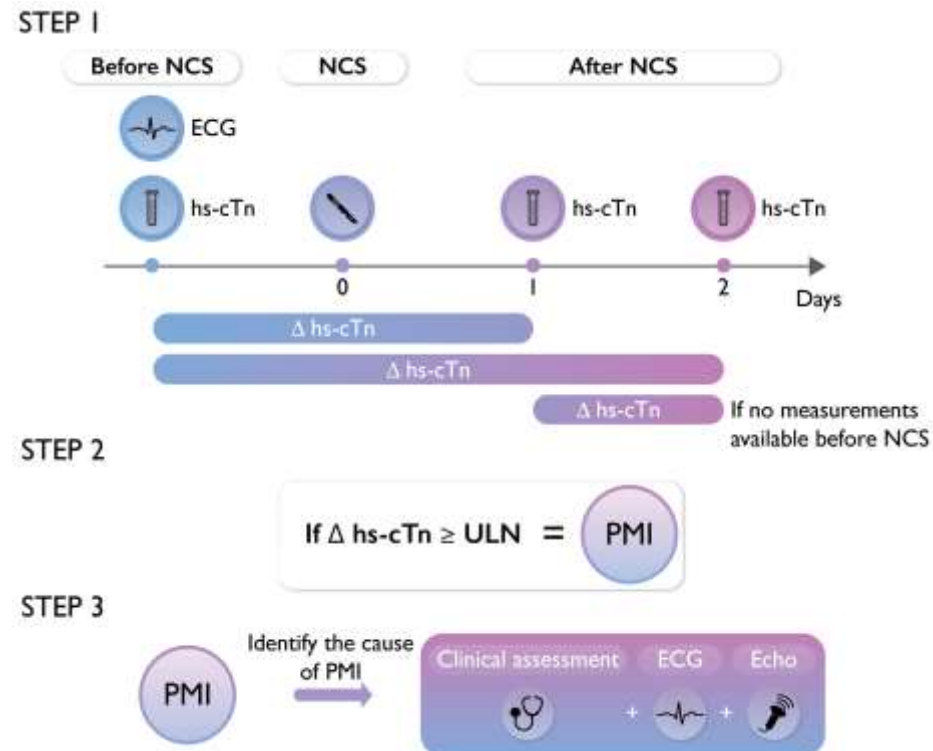


Figure 31-2: Recommended measurements to assess and detect the risk of post-operative cardiac complications.

In patients scheduled to undergo intermediate- or high-risk surgery, pre-operative risk assessment is complemented by ECG, hs-cTn, and BNP/NT-proBNP. An absolute increase in hs-cTn concentration of more than the ULN on days 1 or 2 after surgery compared to the pre-operative level is defined as PMI. In the absence of a pre-operative hs-cTn concentration, a very high hs-cTn concentration on day 1 (e.g., more than five-times the ULN) or a relevant change from day 1 to day 2 (absolute increase or decrease more than the ULN vs. day 1) would also achieve a reliable diagnosis of PMI. Detection of PMI should trigger ECG recording and detailed clinical evaluation for PMI work-up and therapy. The ESC 0/1/2 h algorithm has not been validated for the peri-operative setting and cannot be used here.

Source: 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

General risk-reduction strategies:

| Table 31-5: ESC Recommendations for lifestyle and pharmacological treatment management: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Lifestyle and cardiovascular risk factors: | | |
| Smoking cessation > 4 weeks before NCS is recommended to reduce post-operative complications and mortality ⁽¹⁾ . | I | B |
| Control of CV risk factors -including blood pressure, dyslipidemia, and diabetes- is recommended before NCS. | I | B |
| Initiation of pharmacological treatment: | | |
| In patients with an indication for statins, it should be considered to initiate statins peri-operatively. | IIa | C |
| Pre-operative initiation of beta-blockers in advance ⁽²⁾ of high-risk NCS may be considered in patients who have two or more clinical risk factors ⁽³⁾ , in order to reduce the incidence of peri-operative MI. | IIb | A |
| Pre-operative initiation of beta-blocker in advance of NCS may be considered in patients who have known CAD or myocardial ischemia ⁽⁴⁾ . | IIb | B |
| Routine initiation of beta-blocker peri-operatively is not recommended. | III | A |
| Continuation of pharmacological treatment: | | |

(1) Of the lifestyle changes recommended before surgery, smoking cessation is the best documented in RCTs.

(2) Ideally at least 1 week before surgery, starting with a low dose with dose titration for target heart rate. The target is a resting heart rate 60-70 b.p.m. with a systolic blood pressure > 100 mmHg.

(3) Ischemic heart disease, cerebrovascular disease, renal insufficiency, or DM, according to the RCRI score.

(4) Treatment should ideally be initiated between 30 and (at least) 2 days before surgery, starting at a low dose, and should be continued post-operatively.

| | | |
|--|------------|----------|
| <i>Peri-operative continuation of beta-blockers or statins is recommended in patients currently receiving this medication.</i> | I | B |
| <i>In patients with stable HF, peri-operative continuation of RAAS inhibitors may be considered.</i> | IIb | C |
| Interruption of pharmacological treatment: | | |
| <i>In patients without HF, withholding RAAS inhibitors on the day of NCS should be considered to prevent peri-operative hypotension.</i> | IIa | B |
| <i>For patients on diuretics to treat hypertension, transient discontinuation of diuretics on the day of NCS should be considered.</i> | IIa | B |
| <i>It should be considered to interrupt SGLT-2 inhibitor therapy for at least 3 days before intermediate- and high-risk NCS.</i> | IIa | C |

▪ **Perioperative management of antithrombotic agents:**

Management of patients taking antithrombotic agents and needing surgery or an invasive procedure should consider patient- and procedure-related risk of bleeding and thrombosis. Furthermore, the pharmacokinetic and pharmacodynamic characteristics of the antithrombotic drugs must be considered.

• **Bleeding risk according to type of surgery:**

| Table 31-6: Bleeding risk according to type of non-cardiac surgery: | | |
|--|---|---|
| Surgery with minor bleeding risk | Surgery with low bleeding risk (infrequent or with low impact) | Surgery with high bleeding risk (frequent or with significant impact) |
| <ul style="list-style-type: none"> ○Cataract or glaucoma procedure ○Dental procedures: extractions (1-3 teeth), periodontal surgery, implant positioning, endodontic | <ul style="list-style-type: none"> ○Abdominal surgery: cholecystectomy, hernia repair, colon resection ○Breast surgery ○Complex dental procedures (multiple tooth extractions) | <ul style="list-style-type: none"> ○Abdominal surgery with liver biopsy, extracorporeal shockwave lithotripsy ○Extensive cancer surgery (e.g. pancreas, liver) ○Neuraxial (spinal or epidural) anaesthesia ○Neurosurgery (intracranial, spinal) |

| | | |
|--|--|--|
| <p>(root canal) procedures, subgingival scaling/cleaning</p> <ul style="list-style-type: none"> ○ Endoscopy without biopsy or resection ○ Superficial surgery (e.g. abscess incision, small skin excisions/biopsy) | <ul style="list-style-type: none"> ○ Endoscopy with simple biopsy ○ Gastroscopy or colonoscopy with simple biopsy ○ Large-bore needles procedures (e.g. bone marrow or lymph node biopsy) ○ Non-cataract ophthalmic surgery ○ Small orthopedic surgery (foot, hand arthroscopy) | <ul style="list-style-type: none"> ○ Major orthopaedic surgery ○ Procedures with vascular organ biopsy (kidney or prostate) ○ Reconstructive plastic surgery ○ Specific interventions (colon polypectomy, lumbar puncture, endovascular aneurysm repair) ○ Thoracic surgery, lung resection surgery ○ Urological surgery (prostatectomy, bladder tumor resection) ○ Vascular surgery (e.g. AAA repair, vascular bypass) |
|--|--|--|

- **Antiplatelet management:**

- The management of antiplatelet therapy in patients who have undergone recent PCI and are scheduled for NCS should balance the risk of life-threatening surgical bleeding on antiplatelet therapy against the risk of life-threatening stent thrombosis due to premature DAPT discontinuation.
- Although generally not recommended, bridging with i.v. compounds (Eptifibatide/tirofiban or cangrelor) might be applicable in rare cases when DAPT cannot be interrupted before NCS.

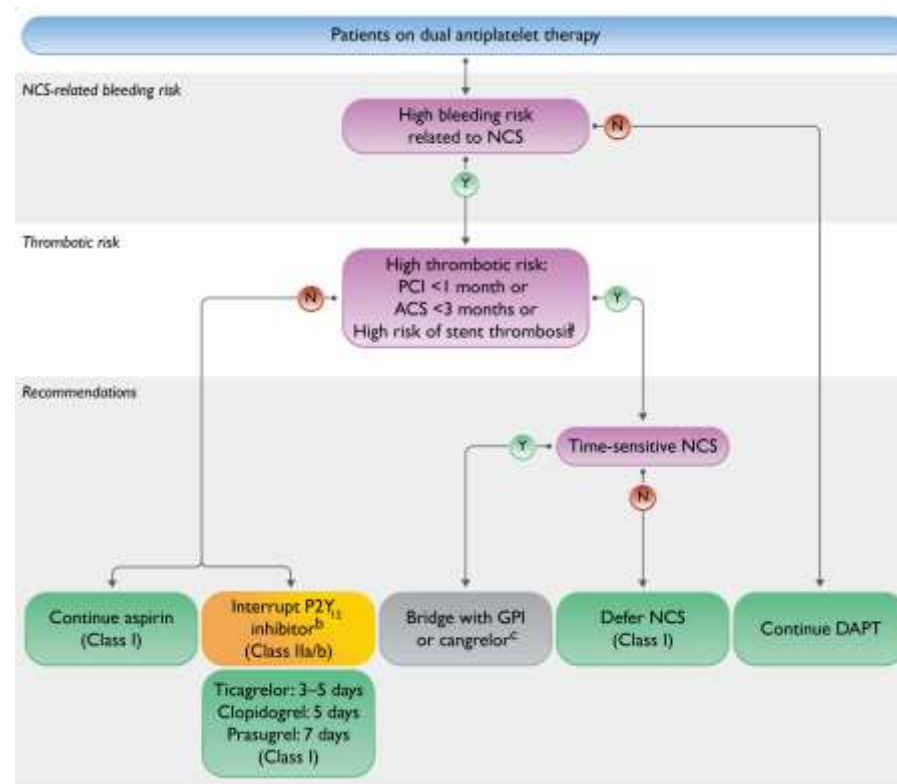


Figure 31-3: Recommendations for management of antiplatelet therapy in patients undergoing non-cardiac surgery. (A) defined by at least one of the following: history of stent thrombosis under antiplatelet therapy, reduced LVEF (< 40%), poorly controlled diabetes, severely impaired renal function/haemodialysis, recent complex PCI (i.e. severely calcified lesion, left main PCI, chronic total occlusion, bifurcational/crush technique, bypass graft PCI), or stent malapposition/residual dissection. **(B)** Timing of resumption after interdisciplinary risk assessment as soon as possible (within 48 h) after surgery. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

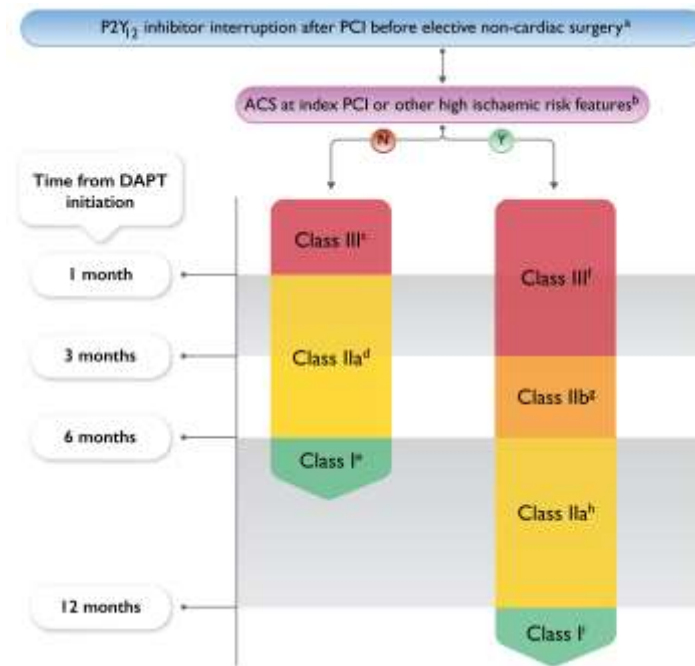


Figure 31-4: P2Y₁₂ inhibitor interruption after PCI before elective non-cardiac surgery. (A) Availability of 24 h cath-lab service is suggested in case of major surgery within 6 months in non-ACS/non-high-risk patients and within 12 months in ACS/high-risk patients. **(B) High risk of peri-operative stent thrombosis** defined by at least one of the following: history of recurrent MI, history of stent thrombosis under antiplatelet therapy, reduced LVEF (<40%), poorly controlled diabetes, severely impaired renal function/haemodialysis, recent complex PCI (i.e. severely calcified lesion, left main PCI, chronic total occlusion, bifurcational/crush technique, bypass graft PCI), stent malapposition/residual dissection. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

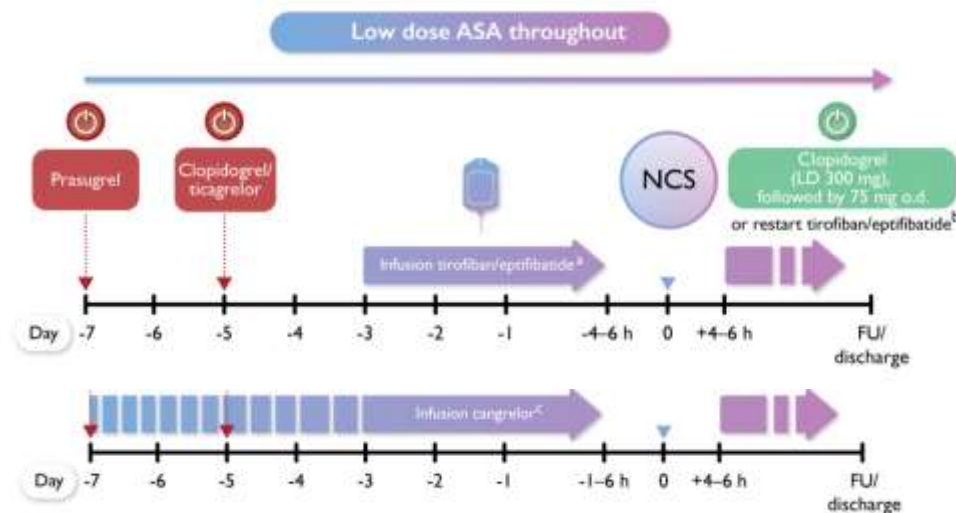


Figure 31-5: Bridging with intravenous antiplatelet agents. (A) Tirofiban: 0.1 µg/kg/min; if Cr. Cl. < 50 mL/min, adjust to 0.05 µg/kg/min. **Eptifibatide:** 2.0 µg/kg/min; if Cr. Cl. is < 50 mL/min, adjust to 1.0 µg/kg/min. **(B) Until oral P2Y12 inhibitor therapy is possible. (C) Initiate within 72 h from P2Y12 inhibitor discontinuation at a dose of 0.75 µg/kg/min for a minimum of 48 h and a maximum of 7 days. Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

Table 31-7: ESC Recommendations for use of antiplatelet therapy in patients undergoing noncardiac surgery:

| Recommendations | Class | Level |
|--|-------|-------|
| Timing of surgery: | | |
| It is recommended to delay elective NCS until 6 months after elective PCI and 12 months after an ACS. | I | A |
| After elective PCI, it is recommended to delay time-sensitive NCS until a minimum of 1 month of DAPT treatment has been given. | I | B |

| | | |
|---|------------|----------|
| <i>In patients with a recent PCI scheduled for NCS, it is recommended that management of antiplatelet therapy is discussed between the surgeon, anaesthesiologist, and cardiologist.</i> | I | C |
| <i>In high-risk patients with a recent PCI (e.g., STEMI patients or high-risk NSTEMI-ACS patients), a DAPT duration of at least 3 months should be considered before time-sensitive NCS.</i> | IIa | C |
| Continuation of medication: | | |
| <i>In patients with a previous PCI, it is recommended to continue aspirin peri-operatively if the bleeding risk allows.</i> | I | B |
| Recommended time interval for drug interruption before NCS: | | |
| <i>If interruption of P2Y12 inhibitor is indicated, it is recommended to withhold ticagrelor for 3-5 days, clopidogrel for 5 days, and prasugrel for 7 days prior to NCS.</i> | I | B |
| <i>For patients undergoing high bleeding risk surgery (e.g. intracranial, spinal neurosurgery, or vitreoretinal eye surgery), it is recommended to interrupt aspirin for at least 7 days pre-operatively.</i> | I | C |
| <i>In patients without a history of PCI, interruption of aspirin at least 3 days before NCS may be considered if the bleeding risk outweighs the ischemic risk, to reduce the risk of bleeding.</i> | IIb | B |
| Resumption of medication: | | |
| <i>If antiplatelet therapy has been interrupted before a surgical procedure, it is recommended to restart therapy as soon as possible (within 48 h) post-surgery, according to interdisciplinary risk assessment.</i> | I | C |

●**Anticoagulation management:**

Peri-operative management of oral anticoagulant therapy depends on surgery- and patient-related factors and the specific OAC agent (VKA or NOAC).

Surgery-related factors include urgency of the intervention and the procedure-related bleeding risk (reflecting both the risk of bleeding occurrence and the risk of adverse outcome if bleeding occurs).

Procedures where mechanical compression is unfeasible carry a high risk of serious bleeding.

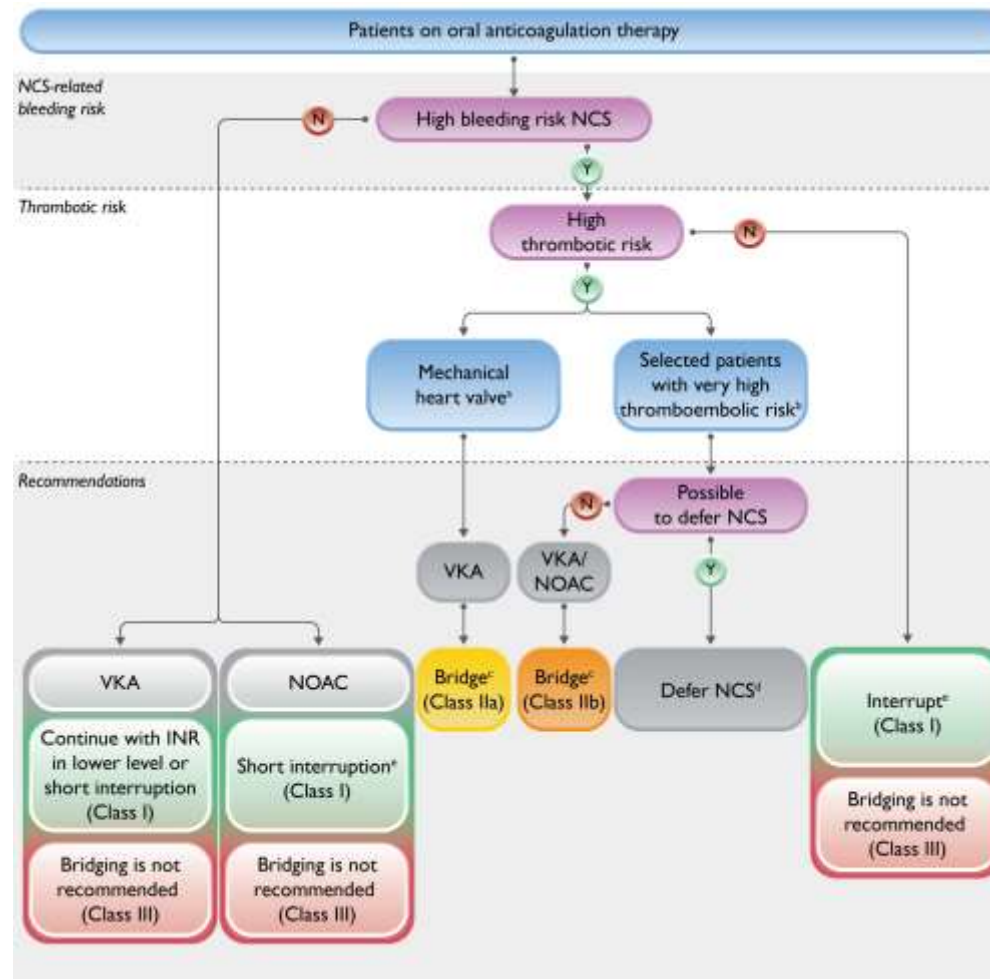


Figure 31-6: Recommendations for management of oral anticoagulation therapy in patients undergoing non-cardiac surgery. (A) Mechanical aortic valve replacement (AVR) and any thromboembolic risk factor (AF, previous thromboembolism, severe LV dysfunction, hypercoagulable state), or older-generation mechanical AVR, or a mechanical mitral valve replacement. (B) Recent stroke < 3 months, high risk of VTE recurrences (e.g., antithrombin 3 deficiency or protein C and/or S deficiency), LV apex thrombus, AF with a very high stroke risk. (C) Bridging with unfractionated heparin or low molecular weight heparin. (D) e.g., > 3 months after stroke/VTE. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

**Timing of last NOAC dose before elective NCS
according to renal function**

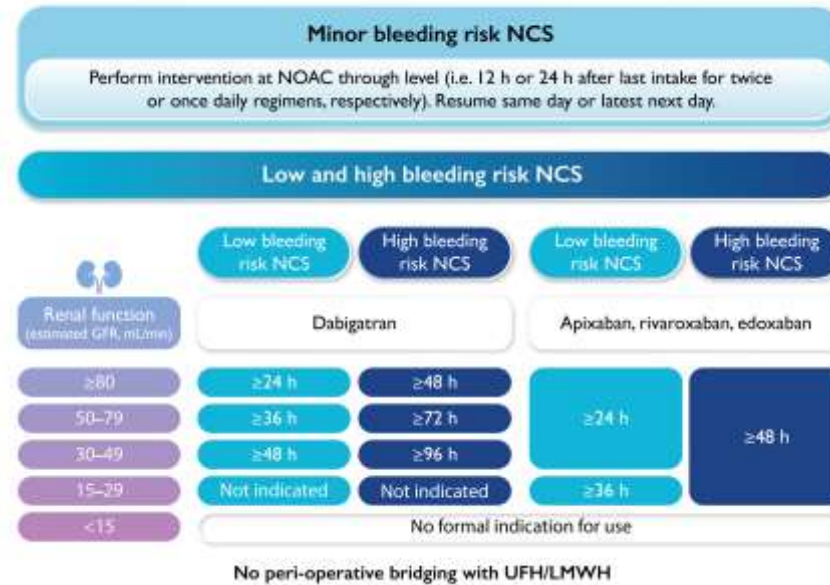


Figure 31-7: Timing of last non-vitamin K antagonist oral anticoagulant dose before elective NCS according to renal function. Source: 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

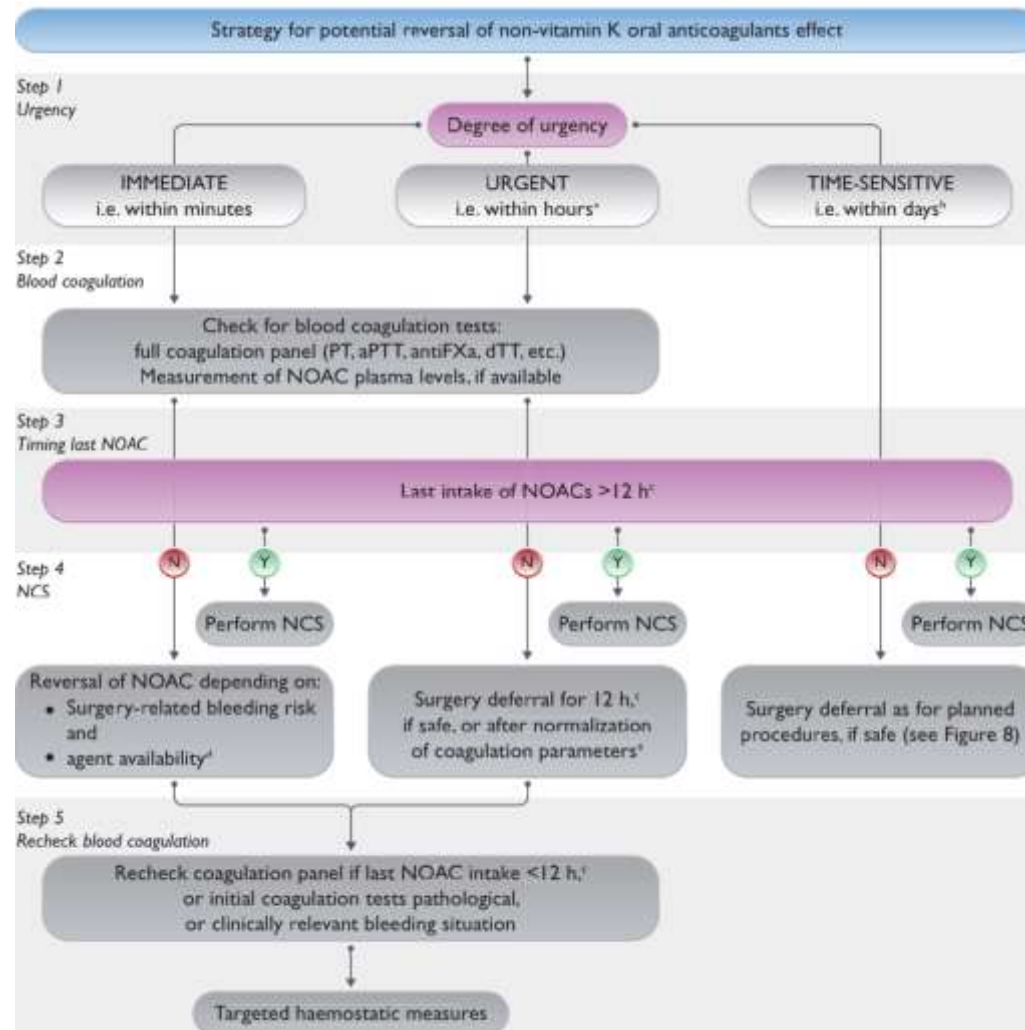


Figure 31-8: Suggested strategy for potential reversal of non-vitamin K oral anticoagulants effect. (A) Conditions that are potentially life-threatening or that may threaten the survival of limb or organ. **(B)** Conditions that can be managed and procedure delayed for several days. **(C)** > 24 h in case of significantly reduced renal function (i.e. eGFR < 50 mL/min). **(D)** If specific reversal agent is unavailable, consider non-specific haemostatic agents (prothrombin complex concentrate [PCC] or activated PCC [aPCCs]). Idarucizumab has only been tested in patients undergoing urgent surgery. Andexanet has not been tested in patients requiring urgent surgery. Andexanet binds all FXa inhibitors (including UFH) nonspecifically. **(E)** Upon re-check. **Source:** 2022 ESC Guidelines on cardiovascular

Table 31-8: ESC Recommendations for interruption and resumption of anticoagulants in patients undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Interruption of anticoagulation: | | |
| <i>When an urgent surgical intervention is required, it is recommended that NOAC therapy is immediately interrupted.</i> | I | C |
| <i>Idarucizumab should be considered in patients on dabigatran and requiring urgent surgical intervention with intermediate to high bleeding risk.</i> | Ila | B |
| <i>In non-minor bleeding risk procedures in patients using a NOAC, it is recommended to use an interruption regimen based on the NOAC compound, renal function, and bleeding risk.</i> | I | B |
| <i>For interventions with a very high risk of bleeding, such as spinal or epidural anaesthesia, interruption of NOACs for up to five half-lives and re-initiation after 24 h should be considered.</i> | Ila | C |
| <i>When specific reversal agents are unavailable, PCC or activated PCC should be considered for reversing NOAC effects.</i> | Ila | C |
| <i>If an urgent surgical intervention is required, specific coagulation tests and assessment of NOAC plasma levels should be considered to interpret routine coagulation tests and waning of anticoagulant effect.</i> | Ila | C |
| Continuation of medication: | | |
| <i>In minor bleeding risk surgery and other procedures where bleeding can be easily controlled, it is recommended to perform surgery without interruption of OAC therapy.</i> | I | B |
| <i>In patients using NOACs, it is recommended that minor bleeding risk procedures are performed at trough levels (typically 12-24 h after last intake).</i> | I | C |

| | | |
|---|------------|----------|
| <i>LMWH is recommended, as an alternative to UFH, for bridging in patients with mechanical heart valves and high surgical risk.</i> | I | B |
| <i>For patients with mechanical prosthetic heart valves undergoing NCS, bridging with UFH or LMWH should be considered if OAC interruption is needed and patients have: (i) mechanical AVR and any thromboembolic risk factor; (ii) old-generation mechanical AVR; or (iii) mechanical mitral or tricuspid valve replacement.</i> | IIa | C |
| <i>Bridging of OAC therapy is not recommended in patients with low/moderate thrombotic risk undergoing NCS.</i> | III | B |
| Start/resumption of medication: | | |
| <i>If bleeding risk with resumption of full-dose anticoagulation outweighs the risk of thromboembolic events, postponing therapeutic anticoagulation 48-72 h after the procedure may be considered, using post-operative thromboprophylaxis until resumption of full OAC dose is deemed safe.</i> | IIb | C |
| <i>Use of reduced-dose NOAC to attenuate the risk of post-operative bleeding is not recommended.</i> | III | C |

- **Thromboprophylaxis:**

- Trends show that the case-fatality of peri-operative VTE has declined over the past few decades. Its causal relationship with preventable mortality has been challenged by a recent meta-analysis. Thus, peri-operative VTE should be regarded as a marker of increased mortality risk rather than a causal factor.
- Careful preoperative assessment is essential to identify patients with increased VTE risk who might benefit from peri-operative thromboprophylaxis. Procedure-related (e.g., type of surgery and likelihood of postoperative immobilization) and patient-related factors contribute to the risk of VTE.
- Patients with CV disease (e.g., patients with recent MI or HF) have increased risk of peri-operative VTE.
- For non-orthopedic surgical patients at low risk of VTE, mechanical methods of VTE prophylaxis (graduated compression stockings, intermittent pneumatic compression, or venous foot pump) rather than pharmacologic prophylaxis or no prophylaxis are recommended.

| Table 31-9: ESC Recommendations for thromboprophylaxis: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended that decisions about peri-operative thromboprophylaxis in NCS are based on individual and procedure-specific risk factors.</i> | I | A |
| <i>If thromboprophylaxis is deemed necessary, it is recommended to choose the type and duration of thromboprophylaxis (LMWH, NOAC, or fondaparinux) according to type of NCS, duration of immobilization, and patient-related factors.</i> | I | A |
| <i>In patients with a low bleeding risk, peri-operative thromboprophylaxis should be considered for a duration of up to 14 or 35 days, for total knee or hip arthroplasty, respectively.</i> | IIa | A |
| <i>NOACs in thromboprophylaxis dose may be considered as alternative treatments to LMWH after total knee and hip arthroplasty.</i> | IIb | A |

- **Patient blood management:**

- Major surgery is associated with a high risk of peri-operative blood loss. Preferred treatment of acute anemia related to peri-operative blood loss is transfusion of allogenic blood products. However, a large body of evidence indicates that inappropriate transfusion of red blood cells (RBCs) may be associated with inherent complications and impaired surgical outcome. Therefore, it is important to identify at-risk patients pre-operatively and manage peri-operative bleeding in any patients undergoing major surgery.
- Iron deficiency (ID) is the underlying cause of anemia in approximately 50% of all cases. A serum ferritin level < 30 ng/mL, transferrin saturation < 20%, and/or microcytic hypochromic red cells (mean corpuscular volume < 80 fl, mean corpuscular

hemoglobin < 27 g/dL) are indicative of ID. In the presence of inflammation or transferrin saturation < 20%, a ferritin level of < 100 ng/mL points to functional ID (iron sequestration).

- A reduction in surgery-related blood loss starts from the preoperative stage, with appropriate cessation strategies for anticoagulation and antiplatelet therapy. Intra-operative approaches to avoid blood loss include: (i) advanced anaesthetic; (ii) advanced surgical techniques with meticulous hemostasis, such as minimally invasive surgery and laparoscopic surgery; (iii) judicious use of diathermy dissection; (iv) physician's mindfulness regarding limiting blood loss; and (v) application of topical hemostatic agents.

| Table 31-10: ESC Recommendations for perioperative complications associated with anemia and blood loss: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Complications associated with anemia: | | |
| <i>It is recommended to measure hemoglobin pre-operatively in patients scheduled for intermediate- to high-risk NCS.</i> | I | B |
| <i>It is recommended to treat anemia in advance of NCS, in order to reduce the need for RBC transfusion during NCS.</i> | I | A |
| <i>The use of an algorithm to diagnose and treat anemic patients before NCS should be considered.</i> | IIa | C |
| Complications associated with blood loss: | | |
| <i>In patients undergoing surgery with expected blood loss of ≥ 500 mL, use of washed cell salvage is recommended.</i> | I | A |
| <i>It is recommended to use point-of-care diagnostics for guidance of blood component therapy, when available.</i> | I | A |
| <i>In patients undergoing NCS and experiencing major bleeding, administration of tranexamic acid should be immediately considered.</i> | IIa | A |
| <i>Use of closed-loop arterial blood sampling systems should be considered to avoid blood loss.</i> | IIa | B |

| | | |
|--|------------|----------|
| <i>Application of meticulous hemostasis should be considered a routine procedure.</i> | Ila | B |
| Complications associated with allogeneic blood transfusion: | | |
| <i>A feedback/monitoring programme or clinical decision support system should be considered to be assessed before blood transfusion.</i> | Ila | B |
| <i>Before allogeneic blood transfusion, it should be considered to obtain an extensive consent about risks associated with transfusion</i> | Ila | C |

Specific diseases:

Patients with CVD have an increased risk of peri-operative CV complications. Both the risk of complications and the peri-operative management depend on the specific type of CVD.

- Coronary artery disease:**

Table 31-11: ESC Recommendations for the timing of non-cardiac surgery and revascularization in patients with known coronary artery disease:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Patients with CCS: | | |
| <i>If PCI is indicated before NCS, the use of new-generation DES is recommended over BMS and balloon angioplasty.</i> | I | A |
| <i>Pre-operative evaluation of patients with an indication for PCI by an expert team (surgeon and cardiologist) should be considered before elective NCS.</i> | Ila | C |
| <i>Myocardial revascularization before high-risk elective NCS may be considered, depending on the amount of ischemic myocardium, refractory symptoms, and findings at coronary angiography (as in the case of left main disease).</i> | Ilb | B |

| | | |
|--|------------|----------|
| <i>Routine myocardial revascularization before low and intermediate-risk NCS in patients with CCS is not recommended.</i> | III | B |
| Patients with ACS: | | |
| <i>If NCS can safely be postponed (e.g., at least 3 months), it is recommended that patients with ACS being scheduled for NCS undergo diagnostic and therapeutic interventions as recommended for ACS patients in general.</i> | I | A |
| <i>In the unlikely combination of a life-threatening clinical condition requiring urgent NCS, and NSTEMI-ACS with an indication for revascularization, the priorities for surgery on a case-by-case basis should be considered by the expert team.</i> | IIa | C |

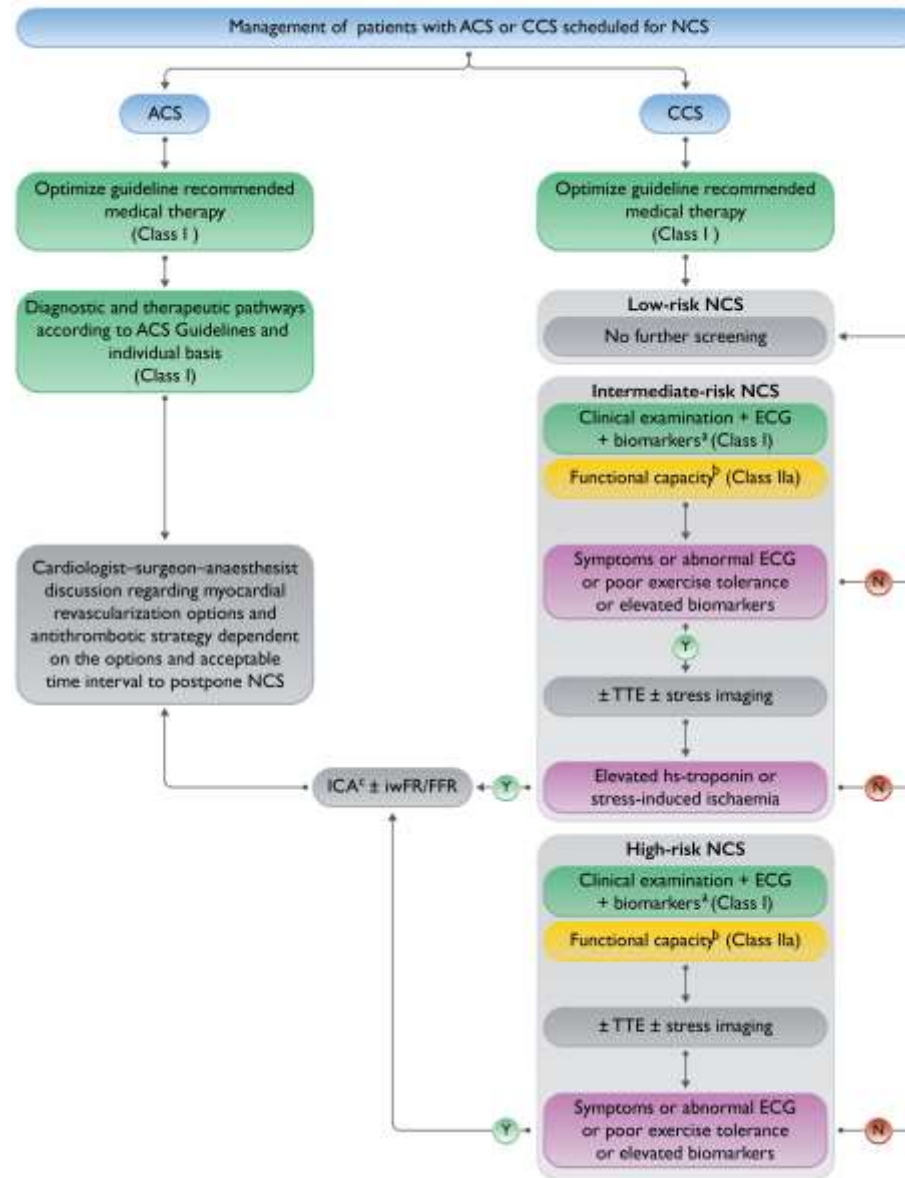


Figure 31-9: Management of patients with acute or chronic coronary syndrome scheduled for non-cardiac surgery. (A) Biomarkers: hs-cTn T/I (Class I) + BNP/NT-proBNP (Class IIa). **(B)** Functional capacity based on Duke Activity Status Index (DASI) or the ability to climb two flights of stairs. **(C)** ICA + PCI/CABG on a case-by-case basis according to the Heart Team. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

- **Chronic heart failure:**

| Table 31-12: ESC Recommendations for management of heart failure in patients undergoing non-cardiac surgery: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>In patients with suspected or known HF scheduled for high-risk NCS, it is recommended to evaluate LV function with echocardiography and measurement of NT-proBNP/BNP levels, unless this has recently been performed.</i> | I | B |
| <i>It is recommended that patients with HF undergoing NCS receive optimal medical treatment according to current ESC guidelines.</i> | I | A |
| <i>In patients with HF undergoing NCS, it is recommended to regularly assess volume status and signs of organ perfusion.</i> | I | C |
| <i>A multidisciplinary team including VAD specialists is recommended for peri-operative management of patients with HF receiving mechanical circulatory support.</i> | I | C |

- **Valvular heart disease:**

Valvular heart disease increases the risk of peri-operative CV complications during NCS. The magnitude of risk is highly variable and depends on the severity of VHD and type of NCS. It is particularly increased in patients with obstructive valve pathology, for example symptomatic AS or MS, where perioperative volume shifts and arrhythmia may lead to rapid decompensation.

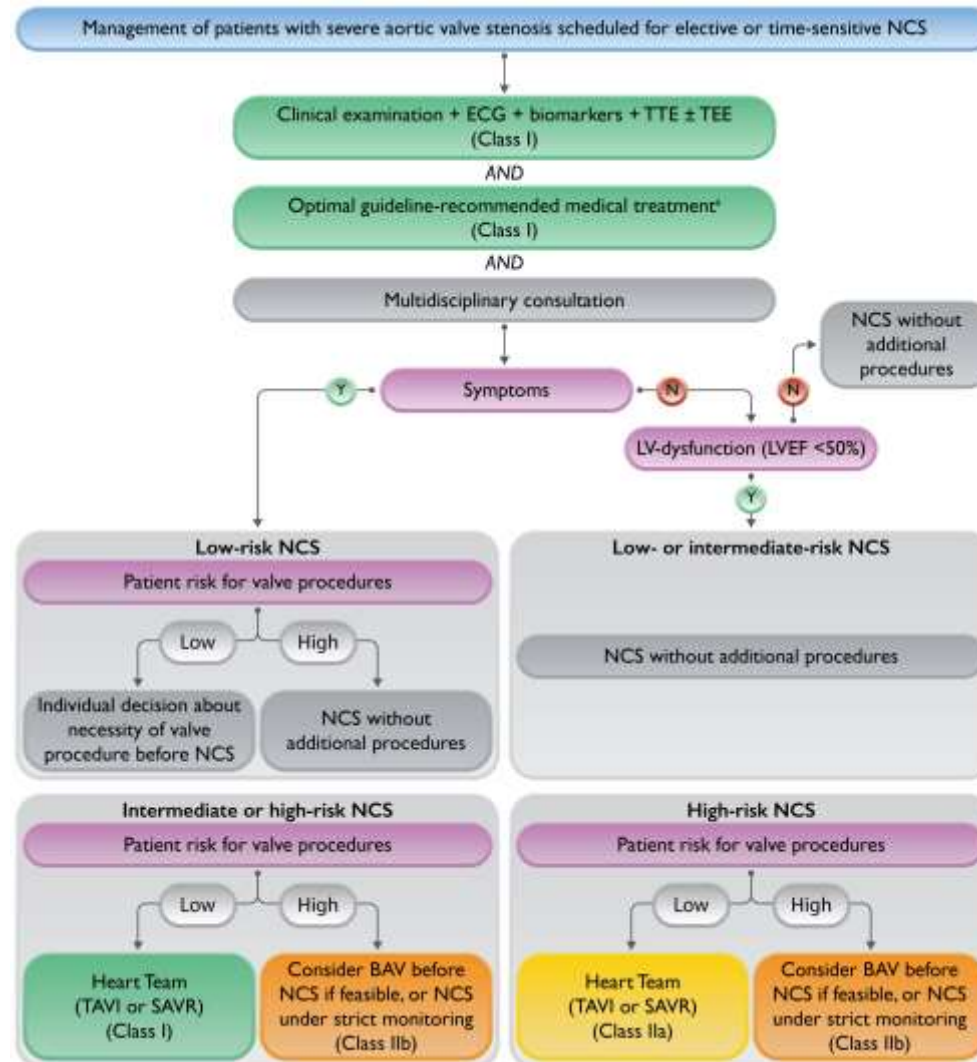


Figure 31-10: Management of patients with severe aortic valve stenosis scheduled for non-cardiac surgery. The figure provides a schematic representation of diagnostic assessment or therapy to be implemented according to surgical risk and underlying cardiac condition. **(A)** This applies to treatment of complications (e.g., AF, HF). No medical therapy is recommended for aortic stenosis per se. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery.

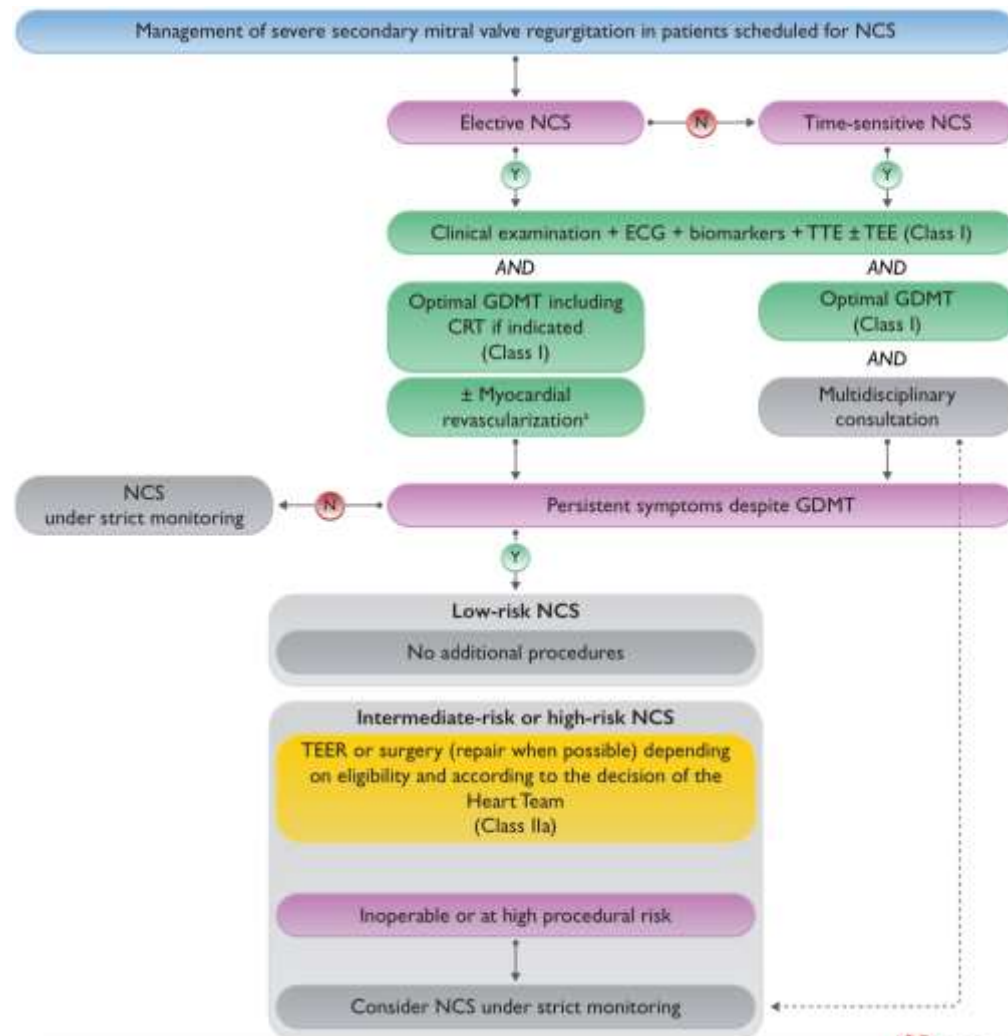


Figure 31-11: Management of patients with secondary mitral valve regurgitation scheduled for non-cardiac surgery. (A) Coronary angiography + PCI/CABG on a case-by-case according to the expert team. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

Table 31-13: ESC Recommendations for management of valvular heart disease in patients undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Clinical and echocardiographic evaluation (if not recently performed) is recommended in all patients with known or suspected VHD who are scheduled for elective intermediate- or high-risk NCS.</i> | I | C |
| Aortic valve stenosis: | | |
| <i>AVR (SAVR or TAVI) is recommended in symptomatic patients with severe AS who are scheduled for elective intermediate- or high-risk NCS.</i> | I | C |
| <i>In asymptomatic patients with severe AS who are scheduled for elective high-risk NCS, AVR (SAVR or TAVI) should be considered after Heart Team discussion.</i> | IIa | C |
| <i>In patients with severe symptomatic AS in need of time-sensitive NCS or in whom the TAVI and SAVR are unfeasible, BAV may be considered before NCS as a bridge to definitive aortic valve repair.</i> | IIb | C |
| Aortic valve regurgitation: | | |
| <i>In patients with symptomatic severe AR <u>or</u> asymptomatic severe AR and LVESD > 50 mm or LVESDi (LVESD/BSA) > 25 mm/m² (in patients with small body size) or resting LVEF ≤ 50%, valve surgery is recommended prior to elective intermediate- or high-risk NCS.</i> | I | C |
| Mitral valve stenosis: | | |
| <i>In patients with moderate-to-severe rheumatic MS and symptoms <u>or</u> SPAP > 50 mmHg, valve intervention (PMC or surgery) is recommended before elective intermediate- or high-risk NCS.</i> | I | C |
| Mitral valve regurgitation: | | |

| | | |
|---|------------|----------|
| <i>In patients with symptomatic severe primary MR or asymptomatic severe primary MR with LV dysfunction (LVESD \geq 40 mm and/or LVEF \leq 60%), valve intervention (surgical or transcatheter) should be considered prior to intermediate- or high-risk NCS, if time allows</i> | Ila | C |
| <i>In patients with severe secondary MR who remain symptomatic despite guideline-directed medical therapy (including CRT if indicated), valve intervention (transcatheter or surgical) should be considered before NCS, in eligible patients with an acceptable procedural risk.</i> | Ila | C |

- **Known or newly diagnosed arrhythmias:**

- Arrhythmias pose a significant burden to patients undergoing NCS, contributing to excessive morbidity and mortality. All patients with known arrhythmia undergoing elective surgery should have a 12-lead ECG performed preoperatively and undergo a cardiology check-up. Prevention of potential arrhythmic triggers is crucial. Patients already taking anti-arrhythmic drugs, in general, should not stop these drugs.
- PVCs and NSVT are frequent in the general population and patients undergoing NCS. Specific clinical features have been suggested as predictors of increasing incidence of PVC. These arrhythmias have historically been considered benign; however, recent studies have suggested that they may be associated with an adverse outcome, even in patients with apparently normal hearts, especially if frequent (e.g., > 10–20%). In patients with heart disease, the prognostic impact of PVC and non-sustained VT depends on type and extent of heart damage. In patients undergoing urgent NCS, they do not require treatment unless frequent and symptomatic.
- Patients with CIEDs can undergo NCS, adequate perioperative device management is needed.

For more details, see Chapter 20 (cardiac Pacing)

Table 31-14: Peri-operative management of patients with arrhythmias:

| | SVT | Idiopathic VT in normal heart | VT in structural heart disease |
|--------------------|------------------|--------------------------------------|---------------------------------------|
| Diagnostics | <i>ECG + TTE</i> | | <i>ECG + TTE + biomarkers</i> |

| | | | |
|---------------------------------|--|--|--|
| | | | <ul style="list-style-type: none"> ○+ Coronary angiography ○+ Cardiac CT/MRI |
| Acute management | <ul style="list-style-type: none"> ○Vagal manoeuvres ○I.v. adenosine, B-blocker,CCB ○Electrical cardioversion if unstable | <ul style="list-style-type: none"> ○Vagal manoeuvres ○I.v. B-blockers/verapamil ○Electrical cardioversion if unstable | <ul style="list-style-type: none"> ○Treatment of underlying heart disease ○I.V. B-blocker (uptitration), amiodarone ○Electrical cardioversion if unstable |
| Prevention of recurrence | <ul style="list-style-type: none"> ○Oral B-blocker, CCB ○Catheter ablation if recurrent despite OMT (only before high-risk NCS) | <ul style="list-style-type: none"> ○ No treatment or ○Oral B-blocker, CCB, class I AAD ○Catheter ablation in case of recurrence despite AADs or drug-intolerance before high-risk NCS | <ul style="list-style-type: none"> ○Oral B-blocker, amiodarone ○Catheter ablation if recurrent despite OMT |

Table 31-15: ESC Recommendations for management of known or newly diagnosed arrhythmias and CIED:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Supraventricular arrhythmias: | | |
| <i>In patients with SVT controlled by medication, it is recommended that AADs are continued during the peri-operative period.</i> | I | C |
| <i>Ablation should be considered in symptomatic patients with recurrent or persistent SVT, despite treatment, prior to high-risk, non-urgent NCS.</i> | IIa | B |

| | | |
|---|------------|----------|
| AF with haemodynamic instability in patients undergoing NCS: | | |
| <i>In AF patients with acute or worsening hemodynamic instability undergoing NCS, emergency electrical cardioversion is recommended.</i> | I | B |
| <i>In AF patients with hemodynamic instability, amiodarone may be considered for acute control of heart rate.</i> | IIb | B |
| Ventricular arrhythmias: | | |
| <i>In patients with symptomatic, monomorphic, sustained VT associated with myocardial scar, recurring despite optimal medical therapy, ablation of arrhythmia is recommended before elective NCS.</i> | I | B |
| <i>It is not recommended to initiate treatment of asymptomatic PVC during NCS.</i> | III | C |
| Bradyarrhythmia and patients carrying cardiac implantable devices: | | |
| <i>If indications for pacing exist, NCS surgery should be deferred, and implantation of a permanent pacemaker should be considered.</i> | IIa | C |
| <i>It is recommended that patients with temporarily deactivated ICDs have continuous ECG monitoring, and during the peri-operative period are accompanied by personnel skilled in early detection and treatment of arrhythmias. In high-risk patients (e.g., pacemaker dependant or ICD patients), or if access to the torso will be difficult during the procedure, it is recommended to place transcutaneous pacing/defibrillation pads prior to NCS.</i> | I | C |
| <i>It is recommended that all patients with CIEDs that are reprogrammed before surgery have a re-check and necessary reprogramming as soon as possible after the procedure.</i> | I | C |
| <i>In high-risk CIED patients (e.g., with ICD or being pacing-dependant) undergoing NCS carrying a high probability of electromagnetic interference (e.g., involving unipolar electrosurgery above the umbilical area), CIED check-up and necessary reprogramming immediately before the procedure should be considered.</i> | IIa | C |

- **Adult congenital heart disease (ACHD):**

ACHD represent an increasing proportion of NCS admissions and might be at high risk of CV events. Pre-operative risk assessment in ACHD needs to focus on the underlying disease, type of surgery, residua, and sequelae. Coexistence of HF, pulmonary hypertension, arrhythmia, hypoxemia, damage to other organs, and endocarditis may considerably influence the baseline risk of these patients from no additional risk to very high risk of worse prognosis.

In a recent report, absolute mortality in ACHD patients undergoing NCS exceeded 4%.

| Table 31-16: Risk stratification for non-cardiac surgery in adults with congenital heart disease | |
|---|--|
| Minor risk | <i>Patients with small, uncorrected defects, and no need for medication or other treatment. Patients with successfully corrected CHD with no symptoms, no relevant residua, and no need for medication</i> |
| Intermediate risk | <i>Patients with corrected or uncorrected conditions with residual hemodynamic abnormality, with or without medication</i> |
| Severe risk | <i>Patients with uncorrected cyanotic heart disease, pulmonary hypertension, other complex CHD, ventricular dysfunction requiring medication, and patients listed for heart transplantation</i> |

Table 31-17: ESC Recommendations for management of patients with adult congenital heart disease undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with ACHD, a consultation with an ACHD specialist is recommended before intermediate- or high-risk surgery.</i> | I | C |

In patients with ACHD, it is recommended that intermediate- and high-risk elective surgery is performed in a centre with experience in the care of ACHD patients.

I C

- **Pericardial diseases:**

Table 31-18: ESC Recommendations for pericardial diseases:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with acute pericarditis, deferring elective NCS until complete resolution of the underlying process should be considered.</i> | IIa | C |
| <i>Avoiding elective NCS procedures under general anaesthesia until colchicine or the immunosuppressive treatment course for pericardial disease is completed may be considered.</i> | IIb | C |

- **Pulmonary disease and pulmonary arterial hypertension:**

Pulmonary arterial hypertension is associated with increased morbidity and mortality in patients undergoing NCS. A meticulous pre-operative diagnostic work-up in this subset of patients should include assessment of functional status and severity of disease, in addition to comorbidities and the type of NCS. In patients with severe PAH, peri-operative mortality ranging between 3-18% has been reported, depending on the severity of the underlying disease, and the nature and urgency of the surgical procedure. Emergency procedures are also associated with a high risk of complications.

Table 31-19: Assessment of peri-operative risk in patients with pulmonary arterial hypertension

| Patient-related peri-operative risk factors | Surgery-related peri-operative risk factors |
|--|--|
| <ul style="list-style-type: none"> • <i>Functional class > II</i> • <i>Reduced six-min walk distance</i> • <i>Coronary heart disease</i> • <i>Previous pulmonary embolism</i> | <ul style="list-style-type: none"> • <i>Emergency surgery</i> • <i>Duration of anaesthesia > 3 h</i> • <i>Intra-operative requirement for vasopressors</i> |

- Chronic renal insufficiency
- Severe RV dysfunction

Table 31-20: ESC Recommendations for patients with pulmonary arterial hypertension undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>It is recommended to continue chronic therapy for PAH in the peri-operative phase of NCS.</i> | I | C |
| <i>It is recommended that hemodynamic monitoring of patients with severe PAH continues for at least 24 h in the post-operative period.</i> | I | C |
| <i>In the case of progression of right HF in the post-operative period in patients with PAH, it is recommended that the diuretic dose be optimized and, if necessary, i.v. prostacyclin analogues be initiated under the guidance of a physician experienced in the management of PAH</i> | I | C |
| <i>Inodilator drugs (dobutamine, milrinone, levosimendan), which increase cardiac output and lower pulmonary vascular resistance, should be considered peri-operatively according to the hemodynamic status of the patient.</i> | Ila | C |

- **Arterial hypertension:**

Postponing surgery is usually not advised in patients with grade 1 or 2 hypertension. In contrast, in subjects with BP \geq 180 and/or 110 mmHg, deferring the intervention until BP is under control is advisable, except for emergency surgery. It also seems important to avoid large peri-operative BP fluctuations.

Table 31-21: ESC Recommendations for pre-operative management of hypertension:

| Recommendations | Class | Level |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|---|------------|----------|
| <i>In patients with chronic hypertension undergoing elective NCS, it is recommended to avoid large peri-operative fluctuations in blood pressure, particularly hypotension, during the peri-operative period.</i> | I | A |
| <i>It is recommended to perform pre-operative screening for hypertension-mediated organ damage and CV risk factors in newly diagnosed hypertensive patients who are scheduled for elective high-risk NCS.</i> | I | C |
| <i>It is not recommended to defer NCS in patients with stage 1 or 2 hypertension.</i> | III | C |

- **Peripheral artery disease (PAD):**

Table 31-22: ESC Recommendations for management of patients with peripheral artery disease and/or abdominal aortic aneurysm undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>In patients with poor functional capacity or significant risk factors or symptoms (such as moderate-to-severe angina pectoris, decompensated HF, valvular disease, and significant arrhythmia), referral for cardiac work-up and optimization is recommended prior to elective surgery for PAD or AAA</i> | I | C |
| <i>Routine referral for cardiac work-up, coronary angiography, or CPET prior to elective surgery for PAD or AAA is not recommended.</i> | III | C |

- **Cerebrovascular disease:**

Patients undergoing NCS should be questioned about previous neurological symptoms, and those with symptoms suggestive of TIA or stroke in the preceding 6 months should undergo pre-operative neurological consultation and neurovascular and brain imaging, if appropriate.

Table 31-23: ESC Recommendations for management of patients with suspected or established carotid artery disease undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Pre-operative carotid artery and cerebral imaging is recommended in patients with a history of TIA or stroke in the previous 6 months and who have not undergone ipsilateral revascularization.</i> | I | C |
| <i>For patients with carotid artery disease undergoing NCS, the same indications for carotid revascularization should be considered as for other patients with carotid stenosis.</i> | IIa | C |
| <i>Pre-operative carotid artery imaging is not recommended routinely in patients undergoing NCS.</i> | III | C |

- **Renal disease:**

Consistently, renal disease portends a significant increase in the post-operative risk of CV events, including MI, stroke, and progression of HF in patients undergoing NCS. For this reason, most risk indices for the quantification of pre-operative risk in patients undergoing NCS include renal function.

Table 31-24: ESC Recommendations for management of patients with renal disease undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with renal disease requiring peri-operative contrast-enhanced radiography, balanced hydration with i.v. isotonic fluids, the use of a minimal volume of contrast media, and the use of low-osmolar or iso-osmolar contrast media should be considered.</i> | IIa | B |
| <i>In patients with known risk factors (age > 65 years, BMI > 30 kg/m², DM, hypertension, hyperlipidemia, CV disease, or smoking) undergoing intermediate- or high-risk NCS, it is</i> | I | C |

| | | |
|---|------------|----------|
| <i>recommended to screen for pre-operative renal disease by measuring serum creatinine and GFR.</i> | | |
| <i>If a cystatin C measurement assay is available, cystatin C measurement should be considered in patients with impaired eGFR (< 45–59 mL/min/1.73 m²) to confirm kidney disease.</i> | Ila | C |

- **Obesity:**

Obesity is defined as a body mass index (BMI) of ≥ 30 kg/m², morbid obesity as a BMI ≥ 35 kg/m², and super-morbid obesity as a BMI ≥ 50 kg/m². Obese individuals have a higher prevalence of CV risk factors and a higher risk of death, and are a population who are at increased risk of adverse events in the case of surgical procedures.

On the one side, there exist specific recommendations for the pre-operative risk assessment of obese patients undergoing NCS, regardless of the presence of pre-existing cardiac condition. On the other side, while obesity accelerates the propensity for CVD, it seems that many types of CVD may have a better prognosis in the overweight population compared with their leaner counterparts, a phenomenon that is known as the “obesity paradox”.

| Table 31-25: ESC Recommendations for management of patients with obesity undergoing noncardiac surgery: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>It is recommended to assess cardiorespiratory fitness to estimate peri-operative CV risk in obese patients, with particular attention to those undergoing intermediate- and high-risk NCS.</i> | I | B |
| <i>In patients at high risk of obesity hypoventilation syndrome, additional specialist investigation before major elective NCS should be considered.</i> | Ila | C |

- **Diabetes:**

The glycated hemoglobin (HbA1c) test should be performed in all patients with diabetes or impaired glucose metabolism scheduled for NCS, if not performed in the previous 3 months.

There is evidence to support that pre-admission optimal treatment of hyperglycemia in patients scheduled for elective NCS is effective in reducing the post operative risk of CV events, including MI, stroke, and progression of HF.

In contrast, no clear association has been shown between intra-operative blood glucose levels and the subsequent risk of surgical site infection, MI, stroke, and death in patients undergoing NCS.

The risk of acidosis associated with metformin use is also debated.

Nevertheless, repeated blood glucose monitoring on the day of surgery is recommended, with a general consensus to maintain peri-operative glucose levels < 10.0 mmol/L without causing hypoglycemia (target level 5.6-10.0 mmol/L). This can be achieved either with subcutaneous doses of rapid-acting insulin analogues or with i.v. insulin.

Table 31-26: ESC Recommendations for management of patients with diabetes mellitus undergoing non-cardiac surgery:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>In patients with diabetes or disturbed glucose metabolism, a pre-operative HbA1c test is recommended, if this measurement has been not performed in the previous 3 months. In case of HbA1c \geq 8.5% (\geq 69 mmol/mol), elective NCS should be postponed, if safe and practical.</i> | I | B |
| <i>A pre-operative assessment for concomitant cardiac conditions is recommended in patients with diabetes with suspected or known CAD, and those with autonomic neuropathy, retinopathy, or renal disease and scheduled to undergo intermediate or high-risk NCS</i> | I | C |

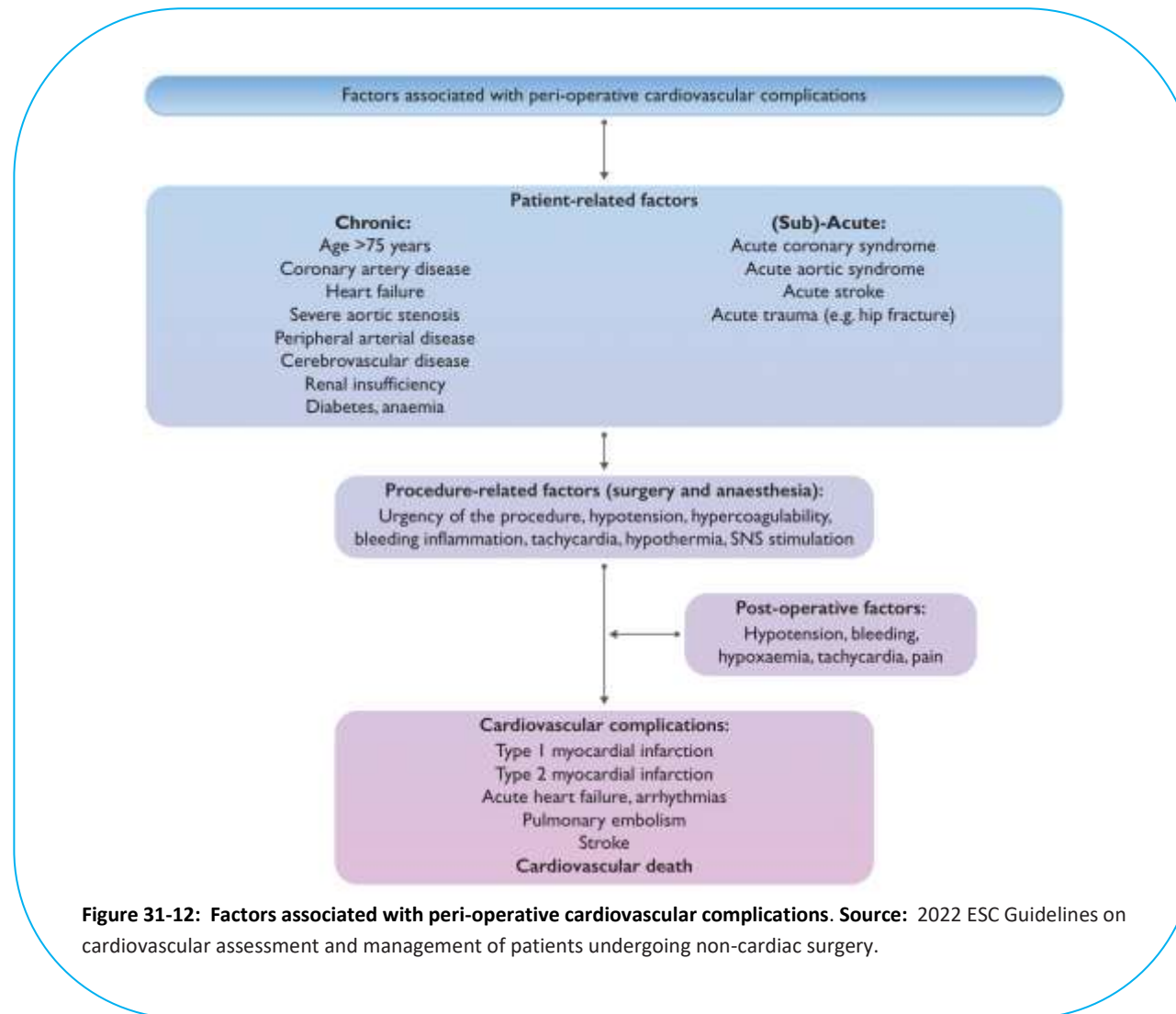
Peri-operative monitoring and anaesthesia:

Table 31-27: ESC Recommendations for peri-operative monitoring and anaesthesia:

| Recommendations | Class | Level |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

| | | |
|---|------------|----------|
| <i>In order to preserve optimal CV stability, it is recommended to apply goal-directed hemodynamic therapy in patients undergoing high-risk NCS.</i> | I | A |
| <i>It is recommended to avoid post-operative acute pain.</i> | I | B |
| <i>In order to minimize the risk of post-operative organ dysfunction, it is recommended to avoid an intra-operative mean arterial pressure decrease of > 20% from baseline values or > 60-70 mmHg for ≥ 10 min.</i> | I | B |
| <i>Non-aspirin NSAIDs are not recommended as first-line analgesics in patients with established or high risk of CVD.</i> | III | B |

Peri-operative cardiovascular complications:



- **Peri-operative myocardial infarction/injury:**

Peri-operative MI (PMI) is defined as acute cardiomyocyte injury (post-operative hs-cTn T/I release) with or without accompanying symptoms, and with or without ECG or imaging evidence of acute myocardial ischemia. Peri-operative MI can only be reliably and rapidly detected using PMI surveillance with hs-cTn before and serially after surgery (e.g. 24 and 48 h postoperatively).

Two major mechanisms underlie perioperative MI:

1. Catecholamine surge, tachycardia, and hypertension increase coronary shear stress, which triggers plaque rupture. This is more likely to happen in plaques with a large atherosclerotic burden even if non-obstructive. Surgery-induced procoagulant state may lead to coronary thrombosis over a ruptured or even a non-ruptured lesion, particularly if the stenosis is tight with a low flow state.
2. Prolonged periods of demand/supply mismatch in patients with severe but previously stable CAD, without any plaque rupture.

To identify the underlying pathophysiology and define causal therapy, systematic work-up and early differentiation of primarily non-cardiac causes (e.g. severe sepsis, PE) vs. the different cardiac causes -including type-1 MI, type-2 MI, tachyarrhythmia, and acute HF- is of major importance. Transthoracic echocardiography is helpful in the work-up of most patients with PMI

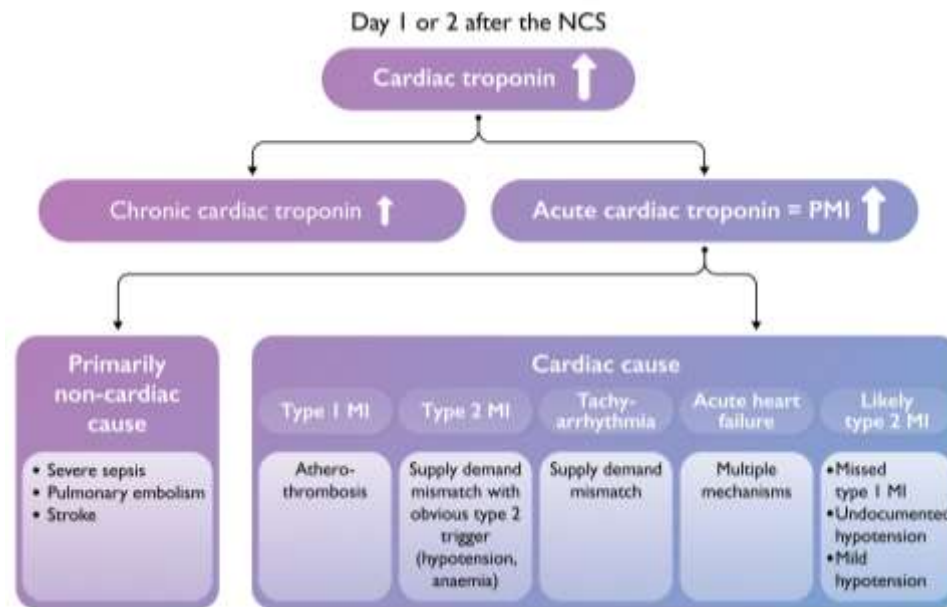


Figure 31-13: Differential diagnosis of elevated post-operative cardiac troponin concentrations. Please be aware that the accuracy of physicians' judgement in the classification of type-1 vs. type-2 MI in the peri-operative setting may be lower vs. the non-operative setting. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

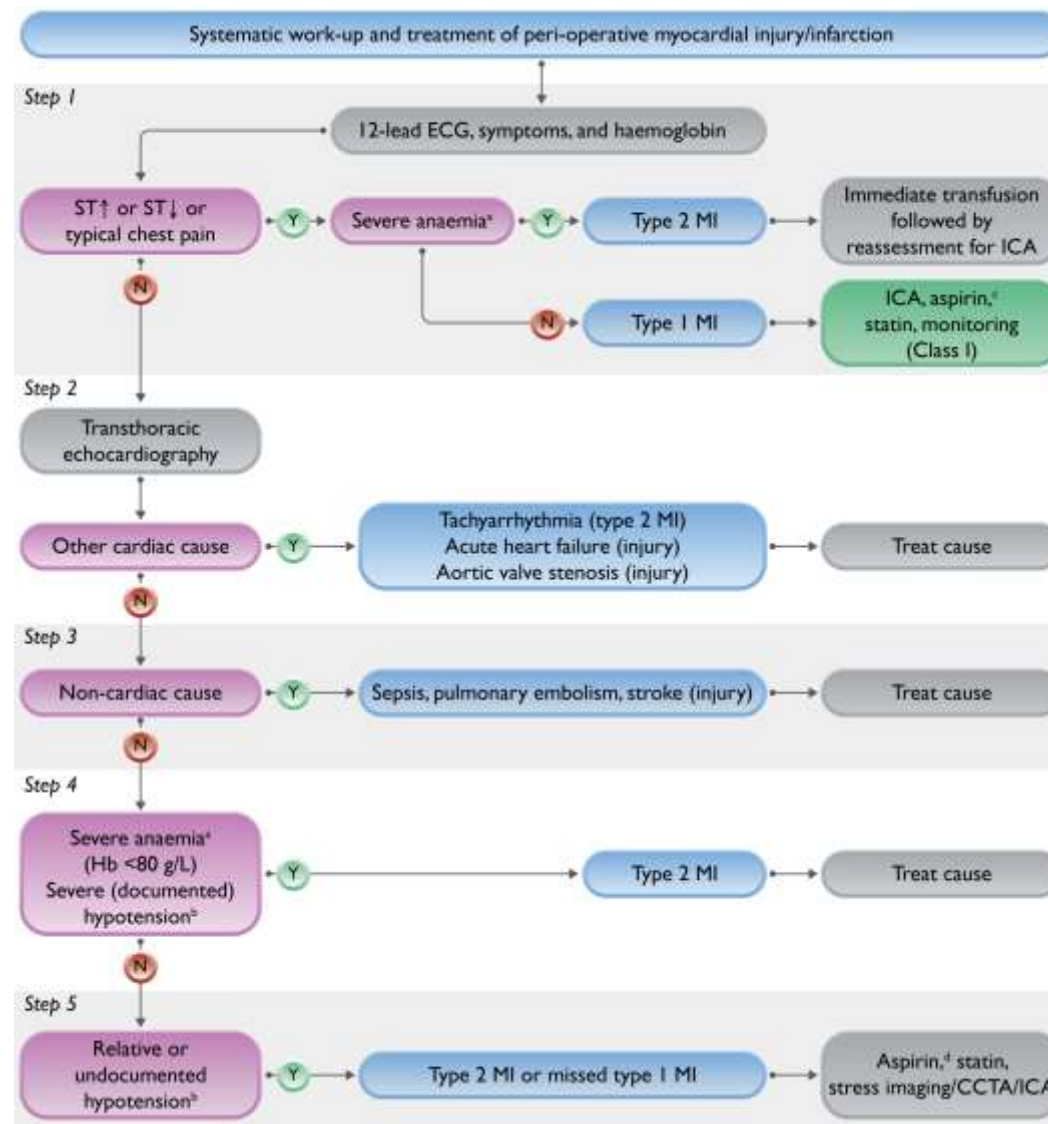


Figure 31-14: Systematic work-up (aetiology) and therapy of peri-operative myocardial infarction/injury. Most patients with type-2 MI and silent type-1 MI should be scheduled for stress imaging or CCTA/ICA as outpatients after discharge, depending on symptoms prior to or after surgery and known CAD. **(A)** Or active bleeding. **(B)** Or other type-2 MI trigger such as hypoxaemia, tachycardia, hypertension. **(C)** Dual antiplatelet therapy after coronary stenting. **(D)** Possibly in combination with dabigatran 110 mg b.i.d. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

- **Atrial fibrillation:**

Post-operative AF is defined as new-onset AF in the immediate postoperative period; its incidence ranges between 2-30%, with peak incidence 2-4 days post-operatively.

Although many post-operative AF episodes are self-terminating and some are asymptomatic, post-operative AF has been associated with a four- to five-fold risk of AF recurrence in the 5 years following cardiac surgery, while the risk of recurrence after NCS is less well described.

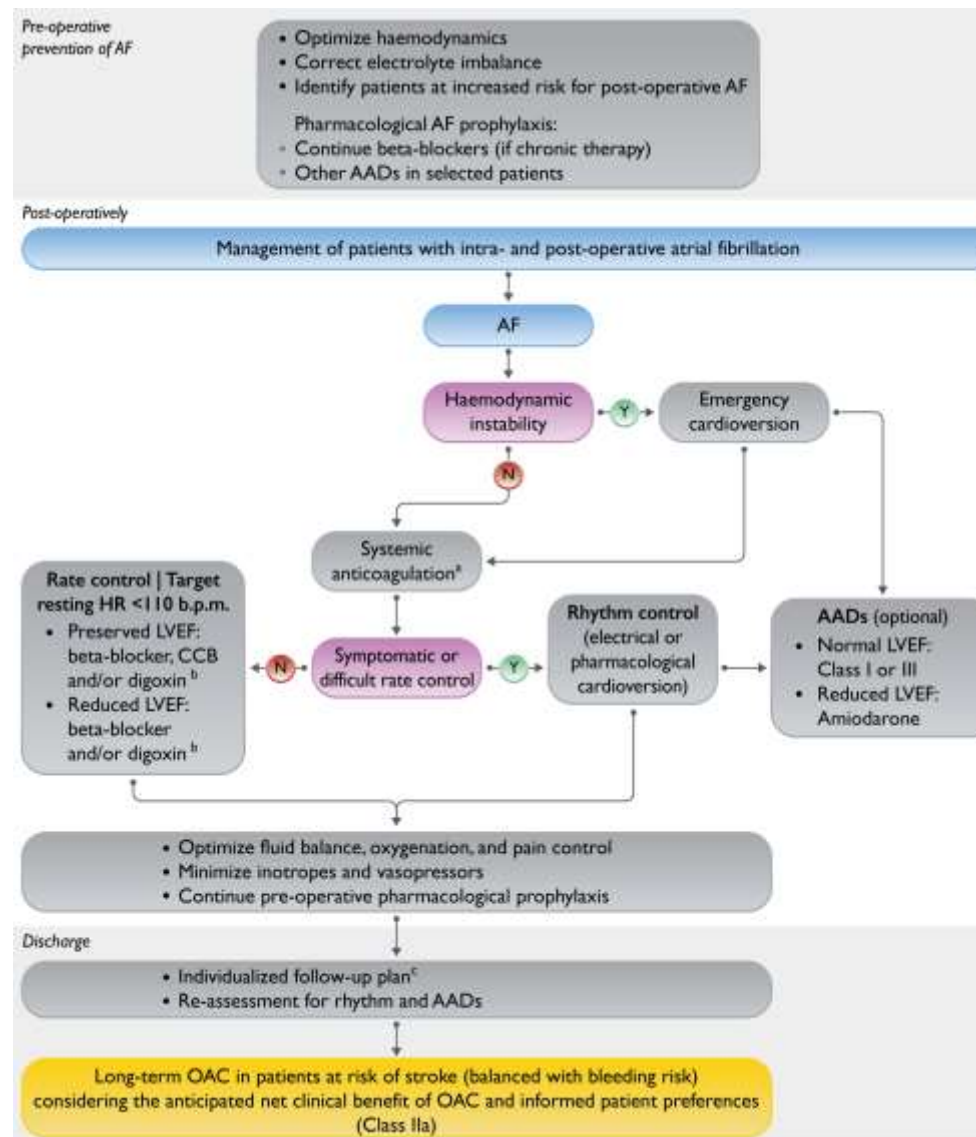


Figure 31-15: Prevention and management of post-operative atrial fibrillation. (A) Depending on the CHA2DS2VASC-score, and postoperative bleeding risk. **(B)** In the acute post-operative phase, unless blood pressure is high, combination of low-dose beta-blocker and loading with digoxin is preferred to avoid hypotension. **(C)** Should include a cardiology visit before month 3. **Source:** 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

- **Peri-operative stroke:**

- Peri-operative stroke is mainly ischaemic or cardioembolic, and AF is often the leading condition.
- With respect to NCS, peri-operative stroke has been reported in 0.08-0.70% of patients undergoing general surgery, 0.2–0.9% of patients requiring orthopaedic surgery, 0.6–0.9% of lung operations, and 0.8–3.0% of surgeries involving the peripheral vasculature.
- The associated mortality ranges from 18- 26%.
- In an attempt to attenuate the risk of peri-operative stroke:
 - Antiplatelet/anticoagulant treatments should be continued whenever possible throughout the peri-operative period. Alternatively, the period of drug withdrawal should be kept as short as possible.
 - Adequate selection of the anaesthetic technique (regional vs. neuraxial vs. general anaesthesia),
 - Prevention and treatment of AF,
 - Euglycaemic control (avoiding both hyperglycaemia and hypoglycaemia), and
 - Meticulous peri-operative control of BP.
- If post-operative stroke occurs, it must trigger immediate action: angio-CT and neurology/neurosurgical consultation with the goal to restore flow in the case of acute thrombotic occlusion.

Table 31-28: ESC Recommendations for peri-operative cardiovascular complications:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>It is recommended to have high awareness of peri-operative CV complications, combined with surveillance for PMI in patients undergoing intermediate- or high-risk NCS.</i> | I | B |
| <i>Systematic PMI work-up is recommended to identify the underlying pathophysiology and define therapy.</i> | I | B |

| | | |
|---|------------|----------|
| <i>It is recommended to treat post-operative STEMI, NSTEMI-ACS, acute HF, and tachyarrhythmias in accordance with guidelines for the non-surgical setting, after interdisciplinary discussion with the surgeon about bleeding risk.</i> | I | C |
| <i>In patients with post-operative PE of high or intermediate clinical probability, initiation of anticoagulation is recommended without delay, while diagnostic work-up is in progress, if bleeding risk is low.</i> | I | C |
| <i>Post-operative oral anticoagulation for PE is recommended to be administered for a period of at least 3 months.</i> | I | C |
| <i>In patients with a post-operative indication for OAC, NOAC is generally recommended over VKA.</i> | I | A |
| <i>In patients with post-operative AF after NCS, long-term OAC therapy should be considered in all patients at risk of stroke, considering the anticipated net clinical benefit of OAC therapy, and informed patient preferences.</i> | IIa | B |
| <i>In patients with Myocardial injury following No cardiac surgery and at low risk of bleeding, treatment with dabigatran 110 mg orally b.i.d. may be considered from 1 week after NCS.</i> | IIb | B |
| <i>Routine use of beta-blocker for the prevention of post-operative AF in patients undergoing NCS is not recommended.</i> | III | B |

References and suggested readings:

- Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery: Developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC) Endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC). *European heart journal*. 2022 Oct 14;43(39):3826-924.
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- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
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Chapter 32:

Cardio-obstetrics

Epidemiology:

In the western world, the risk of CVD in pregnancy has increased due to increasing age at first pregnancy. Maternal heart disease is the major cause of maternal death during pregnancy. Hypertensive disorders are the most frequent CV disorders during pregnancy, occurring in 5-10% of all pregnancies.

Physiological adaptations to pregnancy:

Pregnancy is a dynamic process during which there is a marked increase in metabolic demand and hemodynamic adaptations that vary by trimester and regress toward normal during the postpartum period. The major maternal hemodynamic adaptations during pregnancy include increased cardiac output and plasma volume along with a concurrent reduction in systemic vascular resistance. In light of these rapid and dynamic changes, pregnancy is often considered a physiologic stress test.

- **During the first trimester** (from conception to 13 weeks and 6 days of gestation):
 - Significant decrease in systemic vascular resistance and blood pressure (partially caused by increases in estrogen, progesterone and relaxin levels).
 - 50% increase in renal flow and glomerular filtration rates by the end of the first trimester.
 - To maintain adequate blood pressure in this setting, there is an increased sympathetic and as well as maternal baroreceptor sensitivity. In addition, the RAAS is activated, counteracting the salt and water loss secondary to renal vasodilatation and leading to an increase in heart rate and cardiac output.
- **During the second trimester** (from 14 to 27 weeks and 6 days of gestation): there is a plateau in the reduction in systemic vascular resistance, as relaxin decreases to an intermediate value once the uteroplacental circulation is formed. In addition,

arterial pressures reach a nadir during the second trimester, whereas cardiac output continues to increase to 45% above baseline by 24 weeks.

- **During the third trimester** (from 28 weeks and 0 days of gestation through delivery):
 - There is a peak in cardiac output in the early third trimester and blood pressure begins to increase back to baseline levels.
 - Ratio between plasma volume and red cell mass peaks at 30 to 34 weeks, resulting in a physiologic anemia.
 - Plasma volume increases to 50% greater than nonpregnant values near term, allowing a reserve against blood loss during delivery.
 - Heart rate peaks in the late third trimester, with a 20% to 25% increase relative to baseline.
 - During active labor, SBP and DBP can increase an additional 15-25% and 10-15% respectively.
 - Cardiac output is increased by 15% in early labor and 25% during the active phase.

Pre-pregnancy counselling:

- **Predictors of maternal CV events:**

- Prior cardiac event (heart failure, transient ischaemic attack, stroke, arrhythmia).
- NYHA class III/IV.
- Left heart obstruction (moderate to severe).
- Reduced systemic ventricular systolic function (EF < 40%).
- Reduced subpulmonary ventricular function (TAPSE < 16 mm).
- Systemic atrioventricular valve regurgitation (moderate to severe).
- Pulmonary atrioventricular valve regurgitation (moderate to severe).
- Pulmonary arterial hypertension.
- Cardiac medication before pregnancy.
- Cyanosis (O₂ saturation < 90%)

- Natriuretic peptide levels (NT-proBNP > 128 pg/mL at 20 weeks is predictive of event later in pregnancy)
- Smoking history

• **Predictors of neonatal events:**

- NYHA class III/IV or cyanosis during baseline pre-natal visit
- Maternal left heart obstruction
- Smoking during pregnancy
- Low maternal oxygen saturation (< 90%)
- Multiple gestations
- Use of anticoagulants throughout pregnancy
- Cardiac medication before pregnancy
- 'At birth' cyanotic heart disease
- Mechanical valve prosthesis
- Maternal cardiac event during pregnancy
- Maternal decline in cardiac output during pregnancy
- Abnormal uteroplacental Doppler flow.

Table 32-1: Classification of maternal cardiovascular risk:

| | |
|---------------|--|
| mWHO I | <p>Diagnosis:</p> <ul style="list-style-type: none"> ○ <i>Small or mild (pulmonary stenosis, PDA, MVP)</i> ○ <i>Successfully repaired simple lesions (ASD or VSD, PDA)</i> ○ <i>Atrial or ventricular ectopic beats, isolated</i> <p>Maternal cardiac event rate: 2.5-5%</p> <p>Minimal follow-up visits: <i>Once or twice.</i></p> <p>Care during pregnancy and delivery: <i>Local hospital.</i></p> |
|---------------|--|

| | |
|-------------|---|
| mWHO II | <p>Diagnosis:</p> <ul style="list-style-type: none"> ○ <i>Unoperated ASD or VSD.</i> ○ <i>Repaired tetralogy of Fallot.</i> ○ <i>Most arrhythmias (supraventricular arrhythmias).</i> ○ <i>Turner syndrome without aortic dilatation.</i> <p>Maternal cardiac event rate: 5-10 %</p> <p>Minimal follow-up visits: <i>Once per trimester</i></p> <p>Care during pregnancy and delivery: <i>Local hospital.</i></p> |
| mWHO II:III | <p>Diagnosis:</p> <ul style="list-style-type: none"> ○ <i>Mild left ventricular impairment (EF > 45%)</i> ○ <i>Hypertrophic cardiomyopathy</i> ○ <i>Native or tissue valve disease not considered WHO I or IV (mild MS, moderate AS)</i> ○ <i>Marfan or other HTAD syndrome without aortic dilatation.</i> ○ <i>Aorta < 45 mm in bicuspid aortic valve pathology.</i> ○ <i>Repaired coarctation.</i> ○ <i>Atrioventricular septal defect.</i> <p>Maternal cardiac event rate: 10-19%</p> <p>Minimal follow-up visits: <i>Bimonthly</i></p> <p>Care during pregnancy and delivery: <i>Referral hospital</i></p> |
| mWHO III | <p>Diagnosis:</p> <ul style="list-style-type: none"> ○ <i>Moderate LV impairment (EF 30-45%)</i> ○ <i>Previous peripartum cardiomyopathy without any residual LV impairment</i> ○ <i>Mechanical valve</i> ○ <i>Systemic right ventricle with good or mildly decreased ventricular function</i> |

| | |
|----------------|---|
| | <ul style="list-style-type: none"> ○ <i>Fontan circulation. If otherwise the cardiac condition uncomplicated</i> ○ <i>Unrepaired cyanotic heart disease</i> ○ <i>Other complex heart disease</i> ○ <i>Moderate mitral stenosis</i> ○ <i>Severe asymptomatic aortic stenosis</i> ○ <i>Moderate aortic dilatation (40-45 mm in Marfan syndrome or other HTAD; 45-50 mm in BAV, Turner syndrome ASI 20-25 mm/m², tetralogy of Fallot < 50 mm)</i> ○ <i>Ventricular tachycardia</i> <p>Maternal cardiac event rate: 19-27%</p> <p>Minimal follow-up visits: Monthly or bimonthly</p> <p>Care during pregnancy and delivery: Expert centre for pregnancy and cardiac disease</p> |
| mWHO IV | <p>Diagnosis:</p> <ul style="list-style-type: none"> ○ <i>Pulmonary arterial hypertension</i> ○ <i>Severe systemic ventricular dysfunction (EF < 30% or NYHA class III-IV)</i> ○ <i>Previous peripartum cardiomyopathy with any residual LV impairment.</i> ○ <i>Severe mitral stenosis</i> ○ <i>Severe symptomatic aortic stenosis</i> ○ <i>Systemic RV with moderate or severely decreased ventricular function</i> ○ <i>Severe aortic dilatation (> 45 mm in Marfan syndrome or other HTAD, > 50 mm in bicuspid aortic valve, Turner syndrome ASI > 25 mm/m², tetralogy of Fallot > 50 mm)</i> ○ <i>Vascular Ehlers-Danlos</i> ○ <i>Severe (re)coarctation</i> ○ <i>Fontan with any complication</i> <p>Maternal cardiac event rate: 40-100%</p> |

| | |
|--|---|
| | <p>Minimal follow-up visits: <i>Monthly</i></p> <p>Care during pregnancy and delivery: <i>Expert centre for pregnancy and cardiac disease</i></p> |
|--|---|

Cardiovascular diagnosis in pregnancy:

| Table 32-2: ESC Recommendations for cardiovascular management during pregnancy: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Risk assessment: | | |
| <i>Pre-pregnancy risk assessment and counselling is indicated in all women with known or suspected congenital or acquired cardiovascular and aortic disease.</i> | I | C |
| <i>It is recommended to perform risk assessment in all women with cardiac diseases of childbearing age before and after conception, using the mWHO classification of maternal risk.</i> | I | C |
| <i>It is recommended that high-risk patients are treated in specialized centres by a multidisciplinary pregnancy heart team.</i> | I | C |
| <i>Genetic counselling should be considered in women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease, or genetic malformations associated with CVD.</i> | IIa | C |
| Diagnostic tools: | | |
| <i>Foetal echocardiography by experienced specialists is recommended when there is an elevated risk of foetal abnormalities.</i> | I | C |
| <i>Echocardiography is recommended in any pregnant patient with unexplained or new cardiovascular signs or symptoms.</i> | I | C |
| <i>MRI (without gadolinium) should be considered if echocardiography is insufficient for a definite diagnosis.</i> | IIa | C |

| | | |
|---|------------|----------|
| <i>A chest radiograph may be considered if other methods are not successful in clarifying the cause of dyspnoea.</i> | IIb | C |
| <i>Cardiac catheterization may be considered with very strict indications.</i> | IIb | C |
| <i>CT and electrophysiological studies may be considered in selected patients for vital indications.</i> | IIb | C |
| Cardiac surgery in pregnancy: | | |
| <i>Coronary bypass surgery or valvular surgery may be considered during pregnancy when conservative and medical therapy has failed, and in situations that threaten the mother's life or that are not amenable to percutaneous treatment.</i> | IIb | C |
| <i>If cardiac surgery is to be performed after 24 weeks and before 37 weeks of gestation, then corticosteroids are recommended for the mother.</i> | I | C |
| <i>Delivery before necessary surgery should be considered when gestational age is ≥ 26 weeks.</i> | IIa | C |
| Mode of delivery: | | |
| <i>Vaginal delivery is recommended as the first choice in most patients; for most important exceptions see below.</i> | I | C |
| <i>Induction of labour should be considered at 40 weeks of gestation in all women with cardiac disease.</i> | IIa | C |
| <i>In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.</i> | IIa | C |
| Caesarean delivery should be considered for: obstetrical indications or for patients with: (i) dilatation of the ascending aorta > 45 mm, (ii) with (history of) aortic dissection, (iii) severe aortic stenosis, (iv) pre-term labour while on oral anticoagulants, (v) Eisenmenger's syndrome, or (vi) severe heart failure. | IIa | C |
| <i>Prophylactic antibiotic therapy to prevent endocarditis during delivery is not recommended.</i> | III | C |

| Table 32-3: Cardiovascular contraindications of pregnancy: |
|--|
| Previous peripartum cardiomyopathy with any residual LV impairment. |
| Severe systemic ventricular dysfunction (EF < 30% or NYHA class III-IV). |
| Pulmonary arterial hypertension. |
| Congenital heart disease: |
| <ul style="list-style-type: none"> - Systemic RV with moderate or severely decreased ventricular function. - Fontan with complication (SO₂ < 85%, depressed ventricular function, moderate to severe AV regurgitation, refractory arrhythmia, or protein-losing enteropathy). - Ebstein Anomaly with HF and/or SO₂ < 85%. |
| Valvular heart diseases: |
| <ul style="list-style-type: none"> - Severe mitral stenosis. - Severe aortic stenosis if symptomatic, <u>or</u> impaired LVEF < 50% <u>or</u> symptomatic on exercise test. |
| Aortic diseases: |
| <ul style="list-style-type: none"> - History of aortic dissection. - Severe aortic dilatation (> 45 mm in Marfan syndrome or other HTAD, > 50 mm in bicuspid aortic valve, Turner syndrome ASI > 25 mm/m², tetralogy of Fallot > 50 mm). - Vascular Ehlers-Danlos. - Severe (re)coarctation. |

Congenital heart disease and pulmonary hypertension:

Table 32-4: Risk assessment of pulmonary hypertension and congenital heart diseases during pregnancy:

| Disease | Maternal Risk | Fetal Risk |
|---|--|---|
| Pulmonary hypertension ⁽¹⁾ | <i>Mortality is high. Termination of pregnancy should be discussed.</i> | <i>increased fetal and neonatal mortality (0-30%).</i> |
| Eisenmenger syndrome ⁽²⁾ | <i>Mortality is high (20-50%). Termination of pregnancy should be discussed.</i> | <i>Foetal and neonatal risks are increased. Miscarriage is common.</i> |
| Cyanotic heart disease without pulmonary HTN | <i>HF, thrombosis, arrhythmias, and endocarditis occur in $\geq 15\%$ of cyanotic pregnant patients.</i> | <i>If $SO_2 > 90\%$: better fetal outcome (10% foetal loss). If $SO_2 < 85\%$: fetal growth restriction, prematurity, and fetal death and pregnancy should be discouraged</i> |
| ASD | <i>Repaired ASD: Pregnancy is well tolerated. Unrepaired ASD: Thromboembolic complications (5%), pre-eclampsia and growth restriction.</i> | |
| VSD | <i>Small or repaired VSDs have low-risk of complications</i> | |
| Atrioventricular Septal Defect | <i>The risk of HF is low, and only exists in women with severe regurgitation or impaired ventricular function.</i> | <i>Mortality has been reported in 6% of cases, primarily due to the recurrence of congenital heart disease.</i> |

(1) The greatest period of risk is the puerperium and early post-partum.

(2) Maternal hypoxemia is the most important predictor of outcome. Many of the principles of caring for non-Eisenmenger PAH apply. However, patients with Eisenmenger's syndrome are at increased risk of thrombocytopenia, deficiencies in vitamin K-dependent clotting factors, and bleeding. Caution is therefore needed if prescribing antiplatelet therapy or LMWH.

| | | |
|--|--|---|
| Coarctation of the aorta ⁽¹⁾ | Repair of CoA: Pregnancy is well tolerated. Unrepaired CoA: increased risk of complications including dissection. | |
| Pulmonary valve & RVOT disease ⁽²⁾ | PS is generally well tolerated. However, severe PS may result in RV failure and arrhythmias. | |
| Tetralogy of Fallot ⁽³⁾ | Repaired TOF usually tolerate pregnancy well. Cardiac complications in 8% of repaired patients | The risk of complications is increased, particularly fetal growth restriction |
| Ebstein's anomaly | uncomplicated Ebstein's: well tolerated. Symptomatic patients with cyanosis and/or HF should be counselled against pregnancy. | |
| Transposition of the great arteries | The risks associated with pregnancy are attributable to women with a previous atrial switch, not an arterial switch with increased risk of arrhythmias (sometimes life-threatening) and HF. Patients with more than moderate impairment of RV function or greater than moderate TR should be advised against pregnancy. | The risk of low birth weight and pre-term delivery is 38%. |
| Congenitally corrected TGA | Complications include arrhythmias (AV block) and HF. | The rate of foetal loss is increased, especially if there is cyanosis |

(1) Close surveillance of BP is at least every trimester, is indicated.

(2) In severely symptomatic PS, which is unresponsive to medical therapy and bed rest, percutaneous valvuloplasty can be appropriate.

(3) Maternal screening for 22q11 deletion should be undertaken prior to pregnancy.

| | | |
|--|--|---|
| | <p><i>Some 10% of patients have an irreversible decline in RV function.</i></p> <p><i>Patients in NYHA classes III/IV, with EF <40%, or severe TR should be counseled against pregnancy.</i></p> | |
| Fontan circulation ⁽¹⁾ | <p><i>Patients with a Fontan circulation have an increased risk of fertility issues, but successful pregnancy can occur. However, these are high to very high-risk pregnancies.</i></p> <p><i>Patients with SO₂ < 85%, depressed ventricular function, moderate to severe AV regurgitation, refractory arrhythmia, or protein-losing enteropathy should be counselled against pregnancy.</i></p> | <p><i>Fontan patients have a high-risk of miscarriage (30%).</i></p> <p><i>Antenatal and peripartum bleeding is common.</i></p> <p><i>There is an increased risk of premature birth, small for gestational age, and neonatal death.</i></p> |

Table 32-5: ESC Recommendations for the management of pulmonary hypertension and congenital heart diseases during pregnancy:

| Recommendations | Class | Level |
|--|--------------|--------------|
| Pregnancy and Pulmonary Hypertension: | | |
| <p><i>Right heart catheterization is recommended to confirm the diagnosis of PAH (group 1).</i></p> <p><i>This can be performed during pregnancy but with very strict indications.</i></p> | I | C |

(1) Fontan patients are at risk of thrombo-embolic complications and therapeutic anticoagulation should be considered (balanced with the risk of bleeding). Atrial arrhythmias should be treated promptly, and this often requires electrical cardioversion.

| | | |
|--|------------|----------|
| <i>Treatment dose LMWH is recommended in pregnant patients with chronic thrombo-embolic pulmonary hypertension.</i> | I | C |
| <i>Pregnancy is not recommended in patients with PAH.</i> | III | B |
| <i>If a PAH patient conceives on targeted PH therapies, consideration should be given to withdrawing embryotoxic drugs (endothelin receptor antagonists and riociguat) taking into account the risks of withdrawal.</i> | Ila | C |
| <i>In treatment-naïve pregnant PAH patients, initiating treatment should be considered.</i> | Ila | C |
| Pregnancy and Congenital Heart disease: | | |
| <i>Patients with a systemic right ventricle (Mustard/Senning or congenitally corrected TGA), in NYHA class III/IV, systemic ventricular dysfunction (EF < 40%), or severe TR should be advised against pregnancy.</i> | Ila | C |
| <i>Symptomatic patients with Ebstein's anomaly with saturations < 85% and/or heart failure should be advised against pregnancy.</i> | Ila | C |
| <i>Anticoagulation treatment should be considered during pregnancy in Fontan patients.</i> | Ila | C |
| <i>In patients with a Fontan circulation and saturations < 85%, depressed ventricular function, moderate severe AV regurgitation, refractory arrhythmia, or protein-losing enteropathy, pregnancy is not recommended.</i> | III | C |

Aortic diseases:

Table 32-6: Risk assessment of Aortic diseases during pregnancy:

| | Bicuspid Aortic Valve | Marfan | LoeysDietz | Turner | Vascular Ehlers-Danlos |
|-----------------------------|------------------------------|---------------------------------------|-------------------|-------------------|-------------------------------|
| Location of Aneurysm | <i>Ascending aorta</i> | <i>Everywhere (Sinus of Valsalva)</i> | <i>Everywhere</i> | <i>Everywhere</i> | <i>Everywhere</i> |

| | | | | | |
|--------------------------------------|-----------------------------------|---|---|---|--|
| Risk of dissection | <i>Low: < 1%</i> | <i>High: 1-10%</i> | | | |
| | <i>AS or AR</i> | <i>Dural abnormalities</i> <i>MR</i> <i>HF</i> <i>Arrhythmias</i> | <i>Dural abnormalities</i> <i>MR</i> | <i>Low height</i> <i>Infertility</i> <i>Hypertension</i> <i>Diabetes</i> <i>BAV</i> <i>Coarctation</i> | <i>Dural abnormalities</i> <i>Uterine rupture</i> |
| Advice not to become pregnant | <i>Ascending aorta > 50 mm</i> | <i>Ascending aorta > 45 mm (or > 40 mm in family history of dissection or sudden death)</i> | | <i>ASI > 25 mm/m²</i> | <i>All patients</i> |

| Table 32-7: ESC recommendations for Management of Aortic diseases during pregnancy: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| All aortic diseases: | | |
| <i>It is recommended that women with aortic disease have counselling about the risk of aortic dissection.</i> | I | C |
| <i>Imaging of the entire aorta (CT/MRI) is recommended before pregnancy in patients with a bicuspid aortic valve <u>or</u> genetically proven aortic syndrome <u>or</u> known aortic disease.</i> | I | C |
| <i>When a woman with known aortic dilatation (history of) dissection or genetic predisposition for dissection becomes pregnant, strict blood pressure control is recommended.</i> | I | C |
| <i>Repeated echocardiographic imaging every 4-12 weeks (depending on diagnosis and severity of dilatation) is recommended during pregnancy and 6 months post-partum in patients with ascending aorta dilatation.</i> | I | C |

| | | |
|---|------------|----------|
| <i>For imaging of pregnant women with dilatation of the distal ascending aorta, aortic arch, or descending aorta, MRI (without gadolinium) is recommended.</i> | I | C |
| <i>It is recommended to deliver all women with aortic dilatation or (history of) aortic dissection in an experienced centre with a pregnancy heart team, where cardiothoracic surgery is available.</i> | I | C |
| <i>In patients with an ascending aorta < 40 mm, vaginal delivery is recommended.</i> | I | C |
| <i>In patients with an ascending aorta > 45 mm, caesarean delivery should be considered.</i> | IIa | C |
| <i>In patients with an aorta 40-45 mm, vaginal delivery with epidural anaesthesia and an expedited second stage should be considered.</i> | IIa | C |
| <i>In patients with an aorta 40-45 mm, caesarean section may be considered.</i> | IIb | C |
| <i>In patients with (history of) aortic dissection, caesarean delivery should be considered.</i> | IIa | C |
| <i>Prophylactic surgery should be considered during pregnancy if the aorta diameter is > 45 mm and increasing rapidly.</i> | IIa | C |
| <i>When the foetus is viable, delivery before necessary surgery should be considered.</i> | IIa | C |
| <i>Pregnancy is not recommended in patients: (i) with (or history of) aortic dissection, (ii) with severe dilatation of the aorta (heritable thoracic aortic disease such as Marfan syndrome > 45 mm, bicuspid aortic valve > 50 mm or > 27 mm/m² BSA, or Turner syndrome ASI > 25 mm/m² BSA), (iii) vascular Ehlers–Danlos syndrome.</i> | III | C |
| <i>When possible, the use of ergometrine is not recommended in women with aortic disease.</i> | III | C |
| Specific syndromes: | | |
| <i>In patients with vascular Ehlers-Danlos syndrome, celiprolol ⁽¹⁾ is recommended.</i> | I | C |
| <i>Beta-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases.</i> | IIa | C |

(1) Beta blocker with unique pharmacology: B1 antagonist, B2 partial agonist and weak alpha2 antagonist.

Valvular heart disease:

▪ **Native Valvular Heart diseases:**

In stenotic valve diseases, increased CO causes an increase in transvalvular gradient of 50%, mainly between the first and second trimesters, which increases the risk of maternal and foetal complications.

• **Mitral Stenosis:**

- Mild MS is generally well tolerated.
- HF occurs in one-half of pregnant women with a valve area $\leq 1.5 \text{ cm}^2$, most often during the second trimester, even in the absence of symptoms before pregnancy. Sustained AF, although rare ($< 10\%$), may precipitate HF and thrombo-embolic events.
- All patients with significant MS should be counseled against pregnancy and intervention should be considered pre-pregnancy, favouring percutaneous intervention, even if asymptomatic, and even more so if the valve area is $< 1.0 \text{ cm}^2$.

• **Aortic Stenosis:**

- Cardiac morbidity is related to the baseline severity of AS and symptoms.
- Even in patients with severe AS, pregnancy is often well tolerated if prior exercise tolerance was normal. Pregnancy should not be discouraged in asymptomatic patients, even with severe AS, when LV size and function and the exercise test are normal.
- All symptomatic patients with severe AS or asymptomatic patients with impaired LV function or a pathological exercise test should be counselled against pregnancy, and surgery should be performed pre-pregnancy. During pregnancy in patients who are severely symptomatic despite medical therapy, percutaneous valvuloplasty can be undertaken by an experienced operator.
- Pre-term birth, intrauterine growth retardation, and low birth weight occur in 20-25% of the offspring of mothers with moderate and severe AS, and are increased in severe AS.

• **Mitral and Aortic regurgitation:**

- Women with severe regurgitation and symptoms or compromised LV function are at high-risk of HF.

- HF occurs in 20-25% of women with moderate or severe rheumatic MR.
- Ascending aortic diameters should be measured in women with aortic regurgitation, especially in those with bicuspid valves.
- Acute severe regurgitation is poorly tolerated. In these cases, surgery is sometimes unavoidable during pregnancy. If the foetus is sufficiently mature, delivery should be undertaken prior to cardiac surgery.

| Table 32-8: ESC recommendations for Management of native valvular heart diseases during pregnancy: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Pre-pregnancy evaluation, including echocardiography, and counselling is recommended for any woman with known or suspected valvular disease.</i> | I | C |
| Mitral stenosis: | | |
| <i>Intervention is recommended before pregnancy in patients with MS and valve area < 1.5 cm².</i> | I | C |
| <i>In patients with symptoms or pulmonary hypertension, restricted activities and beta-1-selective blockers are recommended.</i> | I | B |
| <i>Diuretics are recommended when congestive symptoms persist despite beta-blockers.</i> | I | B |
| <i>Therapeutic anticoagulation using heparins or VKA is recommended in case of atrial fibrillation, left atrial thrombosis, or prior embolism.</i> | I | C |
| <i>Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms <u>or</u> systolic pulmonary artery pressure > 50 mmHg despite medical therapy.</i> | IIa | C |
| Aortic stenosis: | | |
| <i>Intervention is recommended before pregnancy in patients with severe aortic stenosis if:</i> | | |
| - They are symptomatic <u>or</u> | I | B |
| - LV dysfunction (LVEF < 50%) is present <u>or</u> | I | C |
| - When they develop symptoms during exercise testing. | I | C |

| | | |
|--|------------|----------|
| <i>Intervention should be considered before pregnancy in asymptomatic patients with severe AS when a fall in blood pressure below baseline during exercise testing occurs.</i> | Ila | C |
| <i>Balloon aortic valvuloplasty should be considered during pregnancy in patients with severe aortic stenosis and severe symptoms.</i> | Ila | C |
| Chronic regurgitant lesions: | | |
| <i>Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation with symptoms of impaired ventricular function or ventricular dilatation.</i> | I | C |
| <i>Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.</i> | I | C |

▪ **Prosthetic Heart Valves:**

• **Choice of valve prosthesis:**

- In young women who wish to become pregnant in the future, the pregnancy heart team should be involved in the choice of a specific prosthesis. The final choice should be made after discussion with the patient.
- Mechanical valves offer excellent haemodynamic performance and long-term durability, but the need for anticoagulation increases maternal and foetal mortality and morbidity, and the risk of major cardiac events during pregnancy is much higher than with bioprosthetic valves. However, bioprosthetic valves in young women are associated with a high-risk of structural valve deterioration resulting in the risk of going through pregnancy with a dysfunctional valve, and eventually in the inevitable need for re-operation.
- In women with mechanical valves, pregnancy is associated with a very high-risk of complications (WHO risk classification III). The main risks are related to the need for anticoagulation therapy (valve thrombosis and hemorrhagic complications). Additional risks are related to ventricular and valvular dysfunction.
- Current evidence (lacking adequate randomized studies) indicates that the use of VKAs throughout pregnancy, under strict INR control, is the safest regimen to prevent valve thrombosis. LMWH is possibly superior to UFH for preventing valve thrombosis.

- Dyspnoea and/or an embolic event are reasons for immediate transthoracic echocardiography to search for valve thrombosis, usually followed by transoesophageal echocardiography.

- **Delivery:**

Planned delivery is necessary. Vaginal delivery requires a prior switch to i.v. heparin. The use of epidural anaesthesia requires a prolonged interruption of anticoagulant therapy, which may contraindicate its use in women with a mechanical prosthesis. A planned caesarean section may therefore be considered as an alternative, especially in patients with a high-risk of valve thrombosis, to keep the time without VKAs as short as possible. Caesarean section should be performed if labour onset occurs while the patient is still on VKAs.

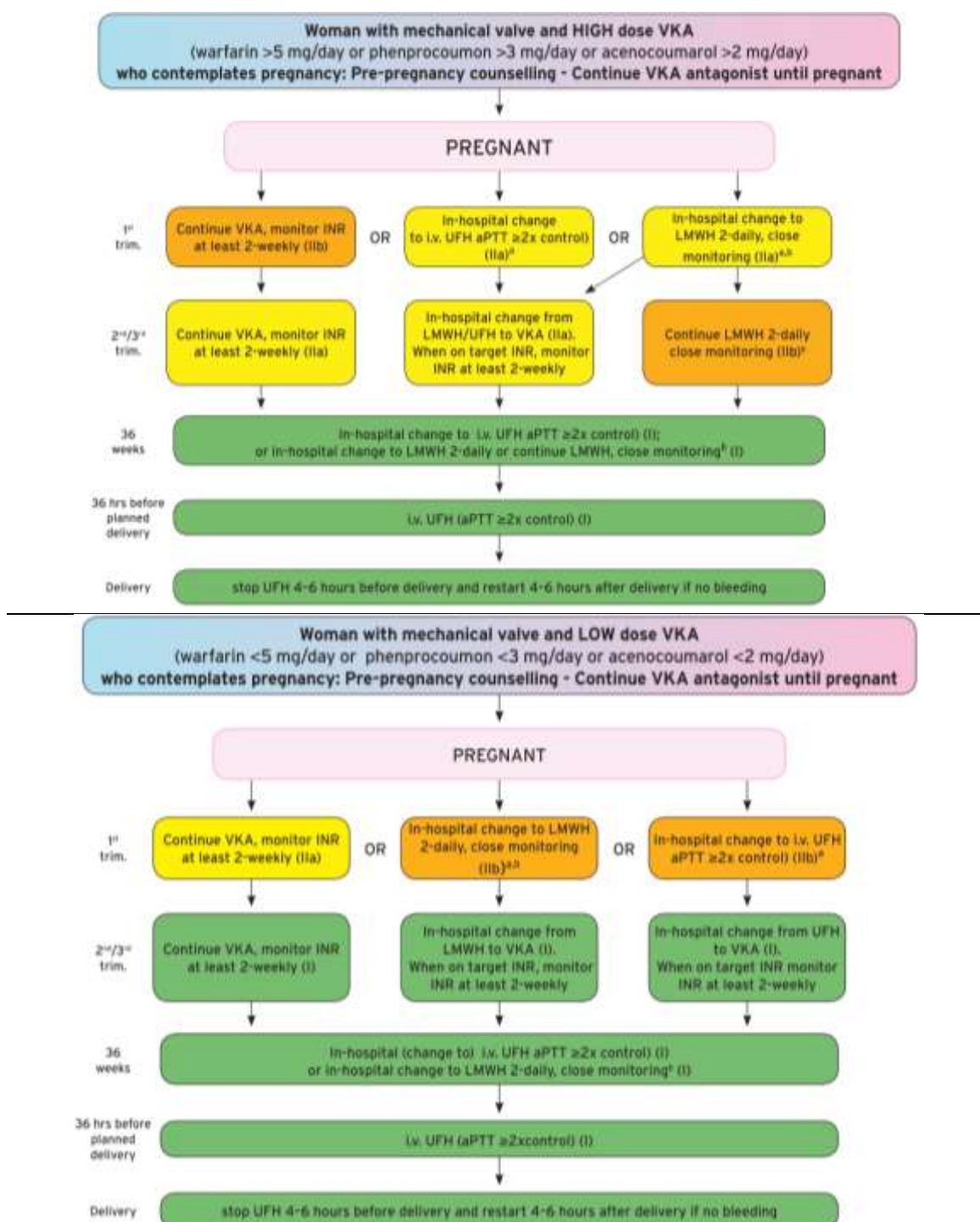


Figure 32-1: Flowchart on anticoagulation in mechanical valves and high-dose VKA (Figure 1) and low-dose VKA (Figure 2). A) 6-12 weeks B) monitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -in-hospital daily anti-Xa levels until target, then weekly (I); -target antiXa levels: 1.0-1.2 U/ml (mitral and right sided valves) or 0.8-1.2 U/ml (aortic valves) 4-6 hrs post-dose (I); -pre-dose anti-Xa levels > 0.6 U/ml (IIb). **Source:** 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy.

Table 32-9: ESC recommendations for Management of prosthetic valvular heart diseases during pregnancy:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>It is recommended that the valve prosthesis for a woman contemplating pregnancy is chosen in consultation with a pregnancy heart team.</i> | I | C |
| <i>A bioprostheses should be considered in young women contemplating pregnancy.</i> | IIa | C |
| <i>It is recommended to manage pregnancy in women with mechanical valves in a centre with a pregnancy heart team.</i> | I | C |
| <i>Immediate echocardiography is recommended in women with mechanical valves presenting with dyspnea and/or an embolic event.</i> | I | C |
| <i>It is recommended to implement changes in the anticoagulation regimen during pregnancy in hospital.</i> | I | C |
| <i>Continuation of VKAs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is < 5 mg/day (or phenprocoumon < 3 mg/day or acenocoumarol < 2 mg/day) after patient information and consent.</i> | IIa | C |
| <i>Discontinuation of VKAs between weeks 6 and 12, and replacement with adjusted-dose intravenous UFH (aPTT ≥ 2x control) or adjusted-dose LMWH twice daily, should be considered in patients with a warfarin dose > 5 mg/day (or phenprocoumon > 3 mg/day or acenocoumarol > 2 mg/day)</i> | IIa | C |
| <i>During the second and third trimesters until the 36th week, VKAs</i> | | |
| <i>- are recommended in women needing a low dose.</i> | I | C |
| <i>- should be considered in women needing a high dose.</i> | IIa | C |
| <i>During the second and third trimesters, LMWH with anti-Xa level monitoring and dose adjustment may be considered in women who need a high dose of VKA after patient information and consent.</i> | IIb | C |

| | | |
|---|------------|----------|
| <i>It is recommended to discontinue VKAs and start adjusted-dose intravenous UFH (aPTT \geq 2x control) or adjusted-dose LMWH at the 36th week of gestation.</i> | I | C |
| <i>It is recommended to replace LMWH with intravenous UFH (aPTT \geq 2x control) at least 36 h before planned delivery. UFH should be continued until 4-6 h before planned delivery and restarted 4-6 h after delivery if there are no bleeding complications.</i> | I | C |
| <i>It is recommended to anticipate the timing of delivery to ensure safe and effective peripartum anticoagulation.</i> | I | C |
| <i>If delivery starts while on a VKA or in less than 2 weeks after discontinuation of a VKA, caesarean section is recommended.</i> | I | C |
| <i>In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose-adjustment (within 36 hrs).</i> | I | C |
| <i>In pregnant women on a VKA, it is recommended to perform INR monitoring weekly or every 2 weeks.</i> | I | C |
| <i>In pregnant women with LMWH, it is recommended to target anti-Xa levels 4-6 h post-dose at 0.8-1.2 U/I (aortic valve prosthesis) or 1.0-1.2 IU/mL (mitral and right-sided valve prostheses)</i> | I | C |
| <i>In pregnant women with LMWH, in addition to monitoring peak anti-Xa levels, monitoring pre-dose levels targeted at \geq 0.6 IU/ mL may be considered.</i> | IIb | C |
| <i>LMWH is not recommended when weekly anti-Xa level monitoring and dose-adjustment is not available.</i> | III | C |

Coronary artery disease:

- Pregnancy is associated with a three- to four-fold increase in AMI risk compared with age-matched non-pregnant women.
- The aetiology of CAD in pregnancy differs from the general population; the majority of CAD has non atherosclerotic mechanisms, including pregnancy-related spontaneous coronary artery dissection (P-SCAD) (43%), angiographically normal coronary arteries (18%), and coronary thrombosis (17%).

- P-SCAD-related AMI occurs most commonly in late pregnancy/early post-partum, and predominantly involves the left-sided coronaries, frequently with multivessel involvement.
- The mechanisms of AMI with angiographically normal coronary arteries remains unclear and include transient coronary spasm (increased vascular reactivity and/or use of ergot derivatives), rather reflecting the limitations of this diagnostic technique.
- Coronary thrombosis in the absence of atherosclerosis is most likely due to the hypercoagulability of pregnancy and can result from paradoxical embolization.

- **Pharmacotherapy:**

- Low-dose aspirin appears to be safe, but there is little information regarding P2Y₁₂ inhibitors. Clopidogrel should be used only when strictly necessary and for the shortest duration.
- In the absence of data regarding glycoprotein IIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor, their use is not recommended.
- Beta-blockade may be beneficial in reducing shear stress in P-SCAD.
- Recombinant tissue plasminogen activator does not cross the placenta but may induce bleeding complications (subplacental bleeding).

- **Intervention:**

The effects of ionizing radiation should not prevent primary PCI in pregnant patients. However, the radiation dose must be minimized.

The majority of reports regarding STEMI in pregnancy relate to baremetal stents. However, new-generation DES are recommended according to the STEMI Guidelines.

The duration of dual antiplatelet therapy with a second/third-generation DES can be shortened, particularly in the absence of great thrombotic burden.

- **Delivery:** Delivery should be postponed (if possible) for at least 2 weeks post-AMI to facilitate maternal management. Vaginal delivery is preferable.

| Table 32-10: ESC recommendations for Management of coronary artery diseases during pregnancy: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>ECG and measurement of troponin levels are recommended when a pregnant woman has chest pain.</i> | I | C |
| <i>Primary coronary angioplasty is recommended as the preferred reperfusion therapy for STEMI during pregnancy.</i> | I | C |
| <i>An invasive management strategy should be considered for NSTEMI-ACS with high-risk criteria.</i> | IIa | C |
| <i>Conservative management should be considered for stable NSTEMI-ACS with low-risk criteria.</i> | IIa | C |
| <i>Follow-up should be considered over at least the next 3 months.</i> | IIa | C |
| <i>Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin due to a lack of data.</i> | III | C |

Cardiomyopathies and heart failure:

• Hypertrophic cardiomyopathy:

Women with HCM usually tolerate pregnancy well.

Fetal mortality by spontaneous abortion (15%), therapeutic abortion (5%), or stillbirth (2%) is comparable to the general population.

Cardioversion should be considered for poorly tolerated persistent AF. Therapeutic anticoagulation is recommended for those with paroxysmal or persistent arrhythmias. Hypovolemia is poorly tolerated. Patients with a past history or family history of sudden death need close surveillance with prompt investigation if they develop symptoms of palpitations or presyncope. When indicated, an ICD should be implanted.

Delivery:

Low-risk cases may have a spontaneous labour and vaginal delivery.

Caesarean section should be considered in patients with severe LVOT obstruction, pre-term labour while on OACs, or severe HF.

Epidural and spinal anaesthesia must be applied cautiously, especially with severe LVOT obstruction, because of potential hypovolemia, and single-shot spinal anaesthesia avoided.

- **Acute HF:**

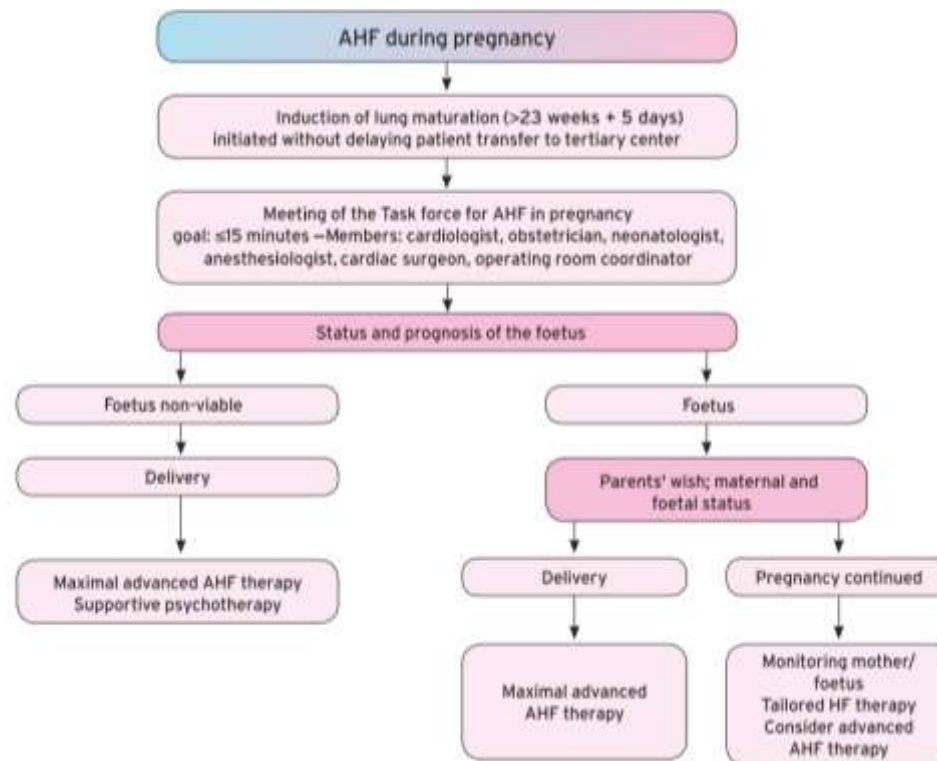


Figure 32-2: Management of acute heart failure during pregnancy: rapid interdisciplinary workup and treatment of mother and foetus. **Source:** 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy modified from Bauersachs et al.

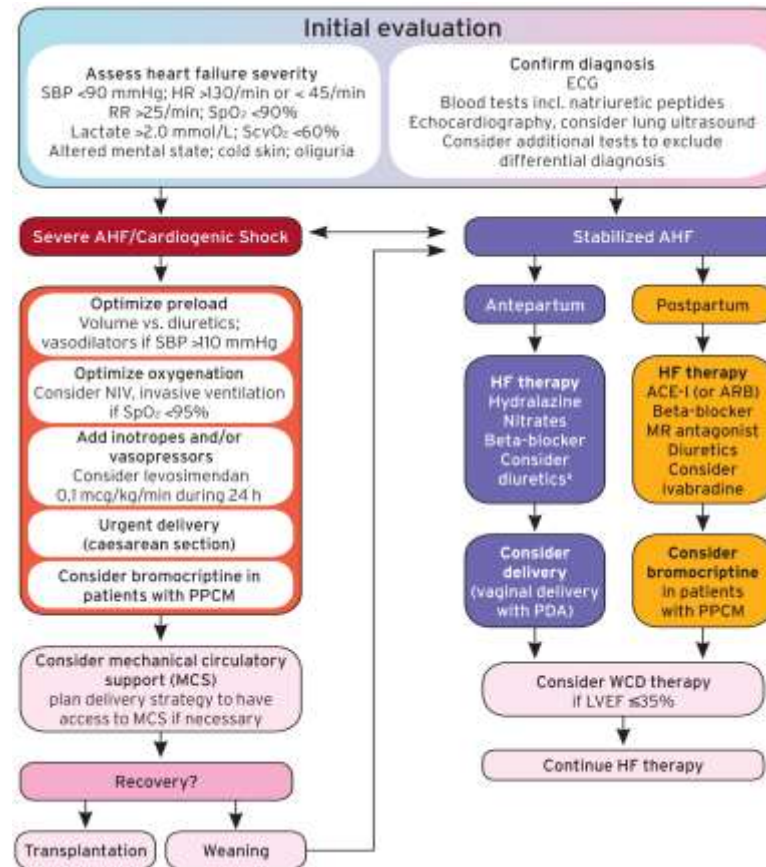


Figure 32-3: Management of acute heart failure during/after pregnancy. A) Diuretics have to be used with caution due to potential reduction in placental blood flow. MCS = mechanical circulatory support; MR= mineralocorticoid receptor; NIV= non-invasive ventilation; PDA = Peridural analgesia; PPCM = peripartum cardiomyopathy; ScvO₂ = central venous oxygen saturation; SpO₂ = peripheral oxygen saturation; WCD = wearable cardioverter-defibrillator. **Source:** 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy modified from Bauersachs et al.

Table 32-11: ESC recommendations for Management of heart failure and cardiomyopathies during pregnancy:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.</i> | I | A |
| <i>It is recommended to treat women with HF during pregnancy according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy.</i> | I | B |
| <i>It is recommended to inform women with HFrEF about the risk of deterioration of the condition during gestation and peripartum</i> | I | C |
| <i>Therapeutic anticoagulation with LMWH or VKA according to the stage of pregnancy is recommended for patients with AF.</i> | I | C |
| <i>In HFrEF, it is recommended that beta-blockers are continued in women who used them before pregnancy or are installed with caution, if clinically indicated</i> | I | C |
| <i>In patients with PPCM and DCM, counselling for recurrence risk during subsequent pregnancy is recommended in all cases, even after recovery of LV function.</i> | I | C |
| <i>As rapid diagnosis and decision-making is crucial for all pregnant women with acute HF, a pre-specified management algorithm and an interdisciplinary team should be established.</i> | IIa | C |
| <i>Patients in cardiogenic shock/dependent on inotropes should be transferred early to a facility where mechanical circulatory support is available.</i> | IIa | C |
| <i>Bromocriptine treatment should be accompanied by prophylactic (or therapeutic) anticoagulation.</i> | IIa | C |
| <i>Due to the high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in patients with severe HF.</i> | IIb | B |

| | | |
|--|------------|----------|
| <i>In patients with PPCM, bromocriptine treatment may be considered to stop lactation and enhance recovery (LV function)</i> | IIb | B |
| <i>In women with PPCM and DCM, subsequent pregnancy is not recommended if LVEF does not normalize.</i> | III | C |
| Cardiomyopathies: | | |
| <i>Pre-pregnancy risk assessment and counselling are recommended in all women using the mWHO classification of maternal risk.</i> | I | C |
| <i>Counselling on safe and effective contraception is recommended in all women of fertile age and their partners.</i> | I | C |
| <i>Counselling on the risk of disease inheritance is recommended for all men and women before conception.</i> | I | C |
| <i>Vaginal delivery is recommended in most women with cardiomyopathies, unless there are obstetric indications for caesarean section, severe heart failure (EF <30% or NYHA class III–IV), or severe outflow tract obstructions, or in women presenting in labour on oral anticoagulants.</i> | I | C |
| <i>It is recommended that medication be carefully reviewed for safety in advance of pregnancy and adjusted according to tolerability in pregnancy.</i> | I | C |
| <i>Therapeutic anticoagulation with LMWH or VKAs according to the stage of pregnancy is recommended for patients with AF.</i> | I | C |
| <i>Continuation of beta-blockers should be considered during pregnancy in women with cardiomyopathies, with close follow-up of foetal growth and of the condition of the neonate, and if benefits outweigh risks.</i> | IIa | C |
| <i>Genetic counselling and testing should be considered in patients with peripartum cardiomyopathy.</i> | IIa | C |

| Table 32-12: ESC Recommendations for Management of arrhythmia during pregnancy: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Acute management of SVT and AF (I.V drugs): | | |
| Vagal maneuvers and if these fails, adenosine are recommended for acute conversion of PSVT. | I | C |
| Immediate electrical cardioversion is recommended for any tachycardia with hemodynamic instability and for pre-excited AF. | I | C |
| Beta-1-selective blockers should be considered for acute conversion of PSVT. | IIa | C |
| Ibutilide or flecainide may be considered for termination of atrial flutter and AF in stable patients with structurally normal hearts ⁽¹⁾ . | IIb | C |
| Long-term management of SVT and AF (Oral drugs): | | |
| Beta-1-selective blockers or verapamil ⁽²⁾ is recommended for the prevention of SVT in patients without pre-excitation on resting ECG | I | C |
| Flecainide or propafenone ⁽³⁾ are recommended for the prevention of SVT in patients with WPW syndrome. | I | C |
| Beta-selective blockers are recommended for rate control of AT or AF | I | C |
| Flecainide, propafenone, or sotalol should be considered to prevent SVT, AT, and AF if AV nodal blocking agents fail. | IIa | C |
| Digoxin and verapamil should be considered for rate control of AT or AF if beta-blockers fail. | IIa | C |

(1) Cardioversion of AF and atrial flutter should generally be preceded by anticoagulation.

(2) AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG or pre-excited AF.

(3) Flecainide and propafenone should be combined with AV nodal blocking agents for certain ATs, but structural heart disease, reduced LV function, and bundle branch block should be excluded.

| | | |
|---|------------|----------|
| <i>Catheter ablation with electroanatomical systems should be considered in experienced centres in cases of drug-refractory and poorly tolerated SVT.</i> | IIa | C |
| Acute management of ventricular tachyarrhythmias (I.V drugs): | | |
| <i>Immediate electrical cardioversion is recommended for sustained both unstable and stable VT.</i> | I | C |
| <i>For acute conversion of sustained, hemodynamically stable, monomorphic VT (e.g. idiopathic VT), a beta-blocker, sotalol, flecainide, procainamide, or overdrive ventricular pacing should be considered.</i> | IIa | C |
| Long-term management of ventricular tachyarrhythmias (Oral drugs): | | |
| <i>ICD (preferably one chamber) is recommended prior to pregnancy if clinically indicated. If indication emerges during pregnancy, ICD implantation is recommended using echocardiographic guidance or mapping, especially if the foetus is beyond 8 weeks of gestation</i> | I | C |
| <i>Beta-blocking agents are recommended during pregnancy and post-partum in patients with long QT syndrome or catecholaminergic polymorphic VT.</i> | I | C |
| <i>Beta-blocking agents or verapamil are recommended for the prevention of idiopathic sustained VT if associated with severe symptoms or hemodynamic compromise.</i> | I | C |
| <i>In idiopathic sustained VT, sotalol ⁽¹⁾ or flecainide should be considered for prevention if other drugs fail.</i> | IIa | C |
| <i>Catheter ablation with electroanatomical mapping systems may be considered in experienced centres in sustained drug-refractory and poorly tolerated VT if there are no other alternatives.</i> | IIb | C |

(1) Class III antiarrhythmic drugs should not be used in patients with prolonged QTc.

Hypertensive disorders:

Hypertensive disorders in pregnancy are the most common medical complications, affecting 5-10% of pregnancies worldwide.

- **Definition:**

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values [SBP \geq 140 mmHg and/or DBP \geq 90 mmHg] and distinguishes mildly (140-159 / 90-109 mmHg) or severely (\geq 160/110 mmHg) elevated BP, in contrast to the grades used by the joint ESC/ESH Hypertension Guidelines.

- **Diagnosis and risk assessment:**

- Repeated BP readings should be performed, preferably on two occasions, \geq 15 min apart in the sitting position (or the left lateral recumbent during labour) with an appropriately-sized arm cuff at heart level.
- Mercury sphygmomanometers are still the gold standard for BP measurement in pregnancy.
- The diagnosis of hypertension in pregnancy by ambulatory BP monitoring (ABPM) is superior to routine BP measurement for the prediction of pregnancy outcome.
- Basic laboratory investigations recommended for monitoring pregnant hypertensive patients include: urinalysis, full blood count, liver enzymes, serum creatinine, and serum uric acid (increased in clinically evident pre-eclampsia, hyperuricemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and foetal outcomes).
- All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia.

- **Classification:** Hypertension in pregnancy is not a single entity but comprises:

- **Pre-existing hypertension:** precedes pregnancy or develops *before 20 weeks* of gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.
- **Gestational hypertension:** develops *after 20 weeks* of gestation and usually resolves within 42 days post-partum.
- **Pre-eclampsia:** *gestational hypertension with significant proteinuria* (> 300 mg/24 h **or** ACR ≥ 30 mg/mmol).
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.

- Antenatally unclassifiable hypertension: this term is used when BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; re-assessment is necessary after 42 days post-partum.

- **Notes about Preeclampsia:**

- Preeclampsia can also manifest in the absence of proteinuria, and additional diagnostic criteria include: **(1)** thrombocytopenia, defined as a platelet count $< 100,000 \times 10^9/L$; **(2)** impaired hepatic function, defined as transaminase level > 2 times the upper limit of normal; **(3)** severe right upper right quadrant or epigastric pain that is not associated with other diagnoses; **(4)** renal insufficiency, defined as serum creatinine > 1.1 mg/dL **or** a doubling of serum creatinine level in the absence of other renal disease; **(5)** pulmonary edema; **(6)** new-onset headache unresponsive to acetaminophen and not associated with other diagnosis or visual symptoms.
- It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with preexisting hypertension, renal disease, or diabetes.
- It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity.
- **HELLP syndrome** is a form of preeclampsia with severe features that generally occurs in the third trimester and has been associated with increased maternal morbidity and mortality. The diagnostic criteria for HELLP are: **(1)** Hemolysis (LDH increased to 60 IU/L or more); **(2)** Elevated Liver enzyme levels (AST and ALT levels increased more than twice the upper limit of normal); **(3)** Low Platelet count ($< 100,000 \times 10^9/L$). Right upper quadrant pain and fatigue are the main presenting symptoms in 90% of cases.
- **Prevention:** Women at high or moderate risk of pre-eclampsia should be advised to take 100-150 mg of aspirin daily from week 12 to weeks 36-37.
- The only cure is delivery.

- **Management:**

Management of hypertension in pregnancy depends on the BP, gestational age, and the presence of associated maternal and foetal risk factors.

There is no evidence currently supporting target BP values in pregnancy.

Most women with pre-existing hypertension and normal renal function have non-severe hypertension (140-159 / 90-109 mmHg) and are at low-risk for cardiovascular complications.

- **Non-pharmacological management:**

Non-pharmacological management of hypertension during pregnancy has a limited role.

Regular exercise might be continued with caution and obese women ($\geq 30 \text{ kg/m}^2$) are advised to avoid a weight gain of more than 6.8 kg.

- **Pharmacological management:** While the goal of treating hypertension is to reduce maternal risk, the agents selected must be effective and safe for the foetus.

- **Severe hypertension:**

Hospitalization if SBP ≥ 170 or DBP ≥ 110 mmHg.

ACE inhibitors, ARBs, and direct renin inhibitors are strictly contraindicated.

Pharmacological treatment with i.v. labetalol, oral methyldopa, or nifedipine should be initiated; i.v. hydralazine is no longer the drug of choice as its use is associated with more perinatal adverse effects than other drugs. However, hydralazine is still commonly used when other treatment regimens have failed to achieve adequate BP control as most obstetricians find its side effect profile acceptable.

Sodium nitroprusside should only be used as the drug of last choice since prolonged treatment is associated with an increased risk of foetal cyanide poisoning.

The drug of choice when pre-eclampsia is associated with pulmonary oedema is nitroglycerin (glyceryl trinitrate), given as an i.v. infusion of 5 micg/min, and gradually to a max. dose of 100 micg/min.

- **Mild-moderate hypertension:**

Despite a lack of evidence, the ESC Guidelines recommend the initiation of drug treatment in all women with persistent elevation of BP 150/95 mmHg and at values $> 140/90$ mmHg in women with:

A. Gestational hypertension (with or without proteinuria)

B. Pre-existing hypertension with the superimposition of gestational hypertension

C. Hypertension with subclinical organ damage or symptoms at any time during pregnancy.

Methyldopa, beta-blockers (most data available for labetalol), and CCBs (most data available for nifedipine) are the drugs of choice.

Beta-blockers appear to be less effective than CCBs and may induce foetal bradycardia, growth retardation, and hypoglycemia; consequently, their type and dose should be carefully selected, with atenolol best avoided.

The plasma volume is reduced in pre-eclampsia, therefore diuretic therapy is best avoided unless in the context of oliguria, when low-dose furosemide may be considered.

I.V. magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures, but should not be given concomitantly with CCBs (there is a risk of hypotension due to potential synergism).

- **Delivery:** Delivery is indicated in pre-eclampsia with visual disturbances or hemostatic disorders, and at 37 weeks in asymptomatic women.

| Table 32-13: ESC recommendations for Management of hypertension during pregnancy: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Low-dose aspirin (100-150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to weeks 36-37. | I | A |
| In women with gestational hypertension <u>or</u> pre-existing hypertension superimposed by gestational hypertension, <u>or</u> with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended at SBP > 140 mmHg or DBP > 90 mmHg. In all other cases, initiation of drug treatment is recommended if SBP ≥ 150 mmHg or DBP ≥ 95 mmHg. | I | C |
| SBP ≥ 170 mmHg or DBP ≥ 110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended. | I | C |

| | | |
|--|------------|----------|
| <i>Methyldopa (B), labetalol (C), and calcium antagonists (C) are recommended for the treatment of hypertension in pregnancy.</i> | I | B |
| <i>In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks.</i> | I | B |
| <i>It is recommended to expedite delivery in pre-eclampsia and with adverse conditions such as visual disturbances <u>or</u> hemostatic disorders.</i> | I | C |
| <i>In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an intravenous infusion is recommended.</i> | I | C |
| <i>In severe hypertension, drug treatment with intravenous labetalol, or oral methyldopa or nifedipine, is recommended.</i> | I | C |
| <i>Limitation of weight gain to < 6.8 kg should be considered in obese women.</i> | IIa | C |
| <i>ACE inhibitors, ARBs, or direct renin inhibitors are not recommended.</i> | III | C |

Venous thrombo-embolic disease during pregnancy and the puerperium:

| Table 32-14: ESC recommendations for Management of venous thromboembolism during pregnancy: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>LMWH is recommended for the prevention and treatment of VTE in pregnant patients.</i> | I | B |
| <i>For high-risk women, it is recommended to give a weight-related prophylactic dose of LMWH (e.g. enoxaparin 0.5 mg/kg once daily)</i> | I | B |
| <i>A documented assessment of risk factors for VTE before pregnancy or in early pregnancy is recommended in all women.</i> | I | C |
| <i>It is recommended that the therapeutic dose of LMWH is based on body weight.</i> | I | C |

| | | |
|---|------------|----------|
| <i>Thrombolytics to manage patients with pulmonary embolism is only recommended in patients with severe hypotension or shock.</i> | I | C |
| <i>In high-risk women, it is recommended to convert LMWH to UFH at least 36 h prior to delivery and stop the UFH infusion 4-6 h prior to anticipated delivery. aPTT should be normal before regional anaesthesia.</i> | I | C |
| <i>In low-risk women on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 h after the last dose of LMWH.</i> | I | C |
| <i>For women after in vitro fertilization complicated by Ovarian hyperstimulation syndrome (OHSS), thromboprophylaxis with LMWH is recommended during the first trimester.</i> | I | C |
| <i>In women who are on antenatal anticoagulation, it should be considered to actively manage the third stage of labour with oxytocin.</i> | IIa | C |
| <i>If compression ultrasound is negative, using magnetic resonance venography should be considered to diagnose pelvic thrombosis before using CT pulmonary angiography or ventilation perfusion scanning.</i> | IIa | C |
| <i>In women on therapeutic LMWH, planned delivery should be considered at around 39 weeks to avoid the risk of spontaneous labour while fully anticoagulated (LMWH is only partially reversed with protamine)</i> | IIa | C |
| <i>Direct oral anticoagulants are not recommended in pregnancy.</i> | III | C |

Cardiovascular drugs and pregnancy:

- **ACE-I, ARB, aldosterone antagonists:** contraindicated during pregnancy.
- **Statins, ezetimibe:** contraindicated.
- **Aspirin** is safe.
- **Clopidogrel:** probably safe, but limited data.
- **Adenosine:** safe
- **β-Blockers** (labetolol, metoprolol) have been extensively and safely used in pregnancy, but may rarely cause intrauterine growth retardation or neonatal hypoglycemia.
Atenolol may be teratogenic and should be avoided. Limited data available for carvedilol.
- **Calcium channel blockers:** less studied than β-blockers, but appear safe. Most experience exists with verapamil and nifedipine.
β-blockers are preferred for arrhythmias.
- **Digoxin:** safe.
- **Diuretics:** may be used to treat HF. Avoid the aggressive use, as they may reduce placental flow.
- **Amiodarone:** crosses the placenta and may cause neonatal goiter. May be used if necessary.
- **Sotalol, flecainide:** relatively safe.
- **Hydralazine, methyldopa:** safe.
- **Nitrates:** may be used in HF, but preferably avoided.

References and suggested readings:

- Vera Regitz-Zagrosek, Jolien W Roos-Hesselink, Johann Bauersachs, et al., ESC Scientific Document Group, 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC), *European Heart Journal*, Volume 39, Issue 34, 07 September 2018, Pages 3165–3241

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- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
- Zipes, D., Libby, P., Bonow, R., Mann, D., Tomaselli, G. and Braunwald, E., 2018. *Braunwald's heart disease*. 11th ed. Elsevier.

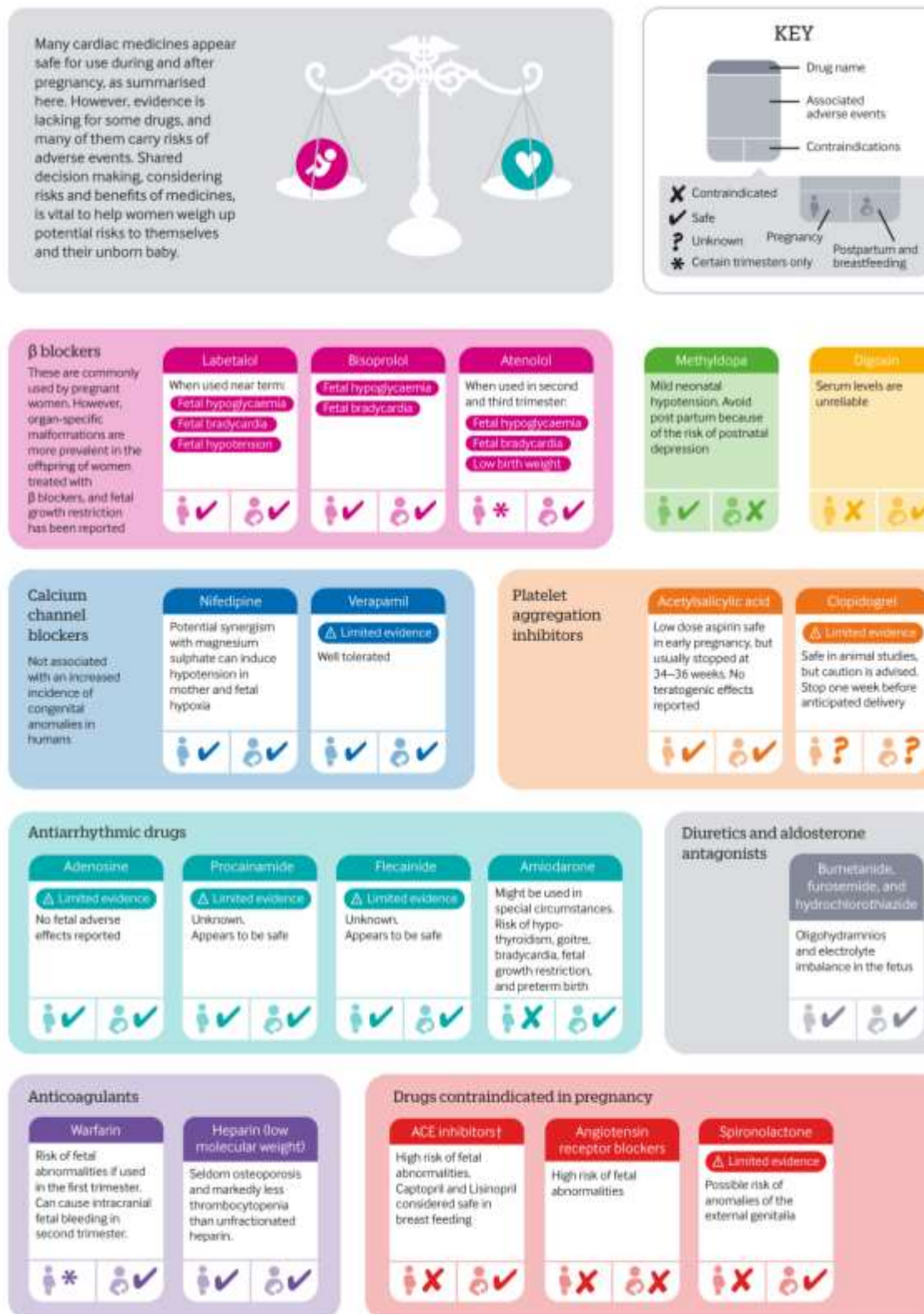


Figure 32-4: Using cardiovascular drugs during pregnancy. Source: Cauldwell M, Dos Santos F, et al. Pregnancy in

Chapter 33:

Cardio-oncology

Since the 1990s, there has been a steady decline in cancer-related mortality mirrored by a steady increase in cancer survivors (CS). In this context, treatment-related side effects have gained more significance. Effective management of patients with both cancer and CVD requires the unique interest and expertise of healthcare providers, which has led to the formation of a new discipline: **cardio-oncology**. The goal of the cardio-oncology discipline is to allow patients with cancer to receive the best possible cancer treatments safely, minimizing cancer therapy-related CV toxicity (CTR-CVT) across the entire continuum of cancer care.

The plan of management for those patients consists of:

- CV risk stratification before cancer therapy initiation.
- Prevention of CV complications during cancer therapy.
- Monitoring of CV toxicity during cancer therapy (Follow-up plan during therapy).
- Management of CV toxicity during cancer therapy.
- CV assessment at the end of cancer therapy.
- Follow-up (First year after cancer treatment and long-term).
- Management in special populations.

Cancer therapy-related CV toxicity (CTR-CVT) definitions:

CTR-CVT includes cancer therapy-related cardiac dysfunction (CTRCD) and other CV toxicities.

Table 33-1: Cancer therapy-related cardiovascular toxicity definitions CTRCD:

| | | |
|--|--------------------|---|
| | Very severe | <i>HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation.</i> |
|--|--------------------|---|

| | | |
|---|-----------------|--|
| Symptomatic CTRCD ⁽¹⁾ | Severe | <i>HF hospitalization.</i> |
| | Moderate | <i>Need for outpatient intensification of diuretic and HF therapy.</i> |
| | Mild | <i>Mild HF symptoms, no intensification of therapy required.</i> |
| Asymptomatic CTRCD | Severe | <i>New LVEF reduction to < 40%.</i> |
| | Moderate | <i>New LVEF reduction by $\geq 10\%$ points to an LVEF of 40-49% OR New LVEF reduction by < 10% points to an LVEF of 40-49% and either new relative decline in GLS by > 15% from baseline or new rise in cardiac biomarkers.</i> |
| | Mild | <i>LVEF $\geq 50\%$ AND new relative decline in GLS by > 15% from baseline and/or new rise in cardiac biomarkers.</i> |

CV risk stratification before cancer therapy:

The optimal time to consider CVD prevention strategies in patients with cancer is at the time of cancer diagnosis and prior to the initiation of cancer treatment.

- **Baseline CV risk assessment:**

Table 33-2: ESC Recommendations for baseline CV assessment modalities before cancer therapy:

| Recommendations | Class | Level |
|---|--------------|--------------|
| History and clinical examination: Oncology patients can be divided into two cohorts with respect to the presence or absence of pre-existing CVD. Although recent SCORE2 and SCORE2-OP tables are not focused | | |

(1) Symptomatic CTRCD represents HF, which is a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) and has traditionally been divided based on the LVEF into: $\leq 40\%$ = HFrEF; 41-49% = HFmrEF; $\geq 50\%$ = HFpEF.

| | | |
|--|-----|---|
| on patients with cancer, risk calculation is recommended for patients with cancer > 40 years of age as a reference to optimize CV risk factors (CVRF) treatment goals. | | |
| ECG: | | |
| An ECG is recommended in all patients starting cancer therapy. | I | C |
| In patients with an abnormal baseline ECG ⁽¹⁾ , referral to a cardiologist is recommended. | I | C |
| Cardiac biomarker: | | |
| Baseline measurement of NP (BNP, NT-pro-BNP) and/or cTn is recommended in all patients with cancer at risk of CTRCD if these biomarkers are going to be measured during treatment to detect CTRCD. | I | C |
| Cardiac imaging: | | |
| Baseline comprehensive TTE is recommended in all patients with cancer at high risk and very high risk of CV toxicity before starting anticancer therapy ⁽²⁾ . | I | C |
| Echocardiography is recommended as the first-line modality for the assessment of cardiac function in patients with cancer. | I | C |
| 3D echocardiography is recommended as the preferred echocardiographic modality to measure LVEF. | I | B |
| GLS is recommended in all patients with cancer having echocardiography, if available. | I | C |
| CMR should be considered for the assessment of cardiac function when echocardiography is unavailable or non-diagnostic. | IIa | C |

(1) Advanced conduction disease (LBBB, RBBB, second degree heart block, severe first-degree heart block with a PR interval > 300 ms); Q waves in two or more contiguous leads; LVH; AF/atrial flutter if previously undiagnosed; QTc prolongation using Fridericia correction formula ($QTcF = QT/\sqrt[3]{VRR}$) > 450 ms for men and > 460 ms for women or other ECG abnormality raising concern.

(2) Except asymptomatic patients referred to breakpoint cluster region-Abelson oncogene locus therapy (BCR-ABL) where baseline TTE should be considered.

Multigated acquisition (MUGA) may be considered when TTE is not diagnostic and CMR is not available.

IIb

C

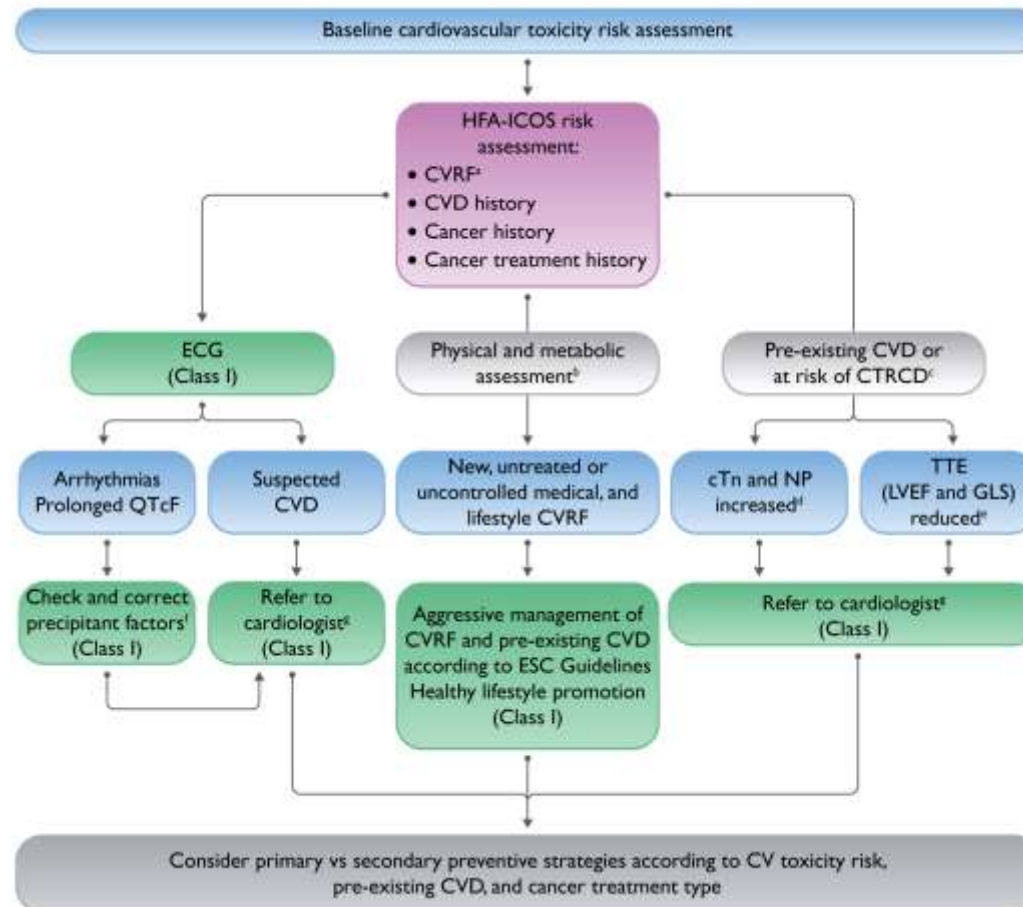


Figure 33-1: Baseline cardiovascular toxicity risk assessment before anticancer therapy. (A) When assessing CVRF, include information about unhealthy lifestyle including sedentary behaviour, smoking, and alcohol intake. (C) According to cancer treatment and HFA-ICOS risk assessment. (D) cTnI/T > 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL. (E) Patients with baseline LVEF < 50% or in the low normal range (LVEF 50-54%) should be referred to a specialized cardiologist or cardio-oncologist. When TTE is used, ideally three-dimensional-LVEF and GLS should be measured. If GLS assessment is not available, other markers of longitudinal function (e.g., annular Doppler velocity) should be considered. Cardiac MRI should be considered if echocardiography is of non-diagnostic quality. (F) Anaemia, infections, electrolyte abnormalities, metabolic problems, other QTc-prolonging drugs. (G) Cardio-oncology referral is recommended when available; alternatively, patients should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer. **Source:** 2022 ESC Guidelines on cardio-oncology

• General approach to CV toxicity risk in patients with cancer:

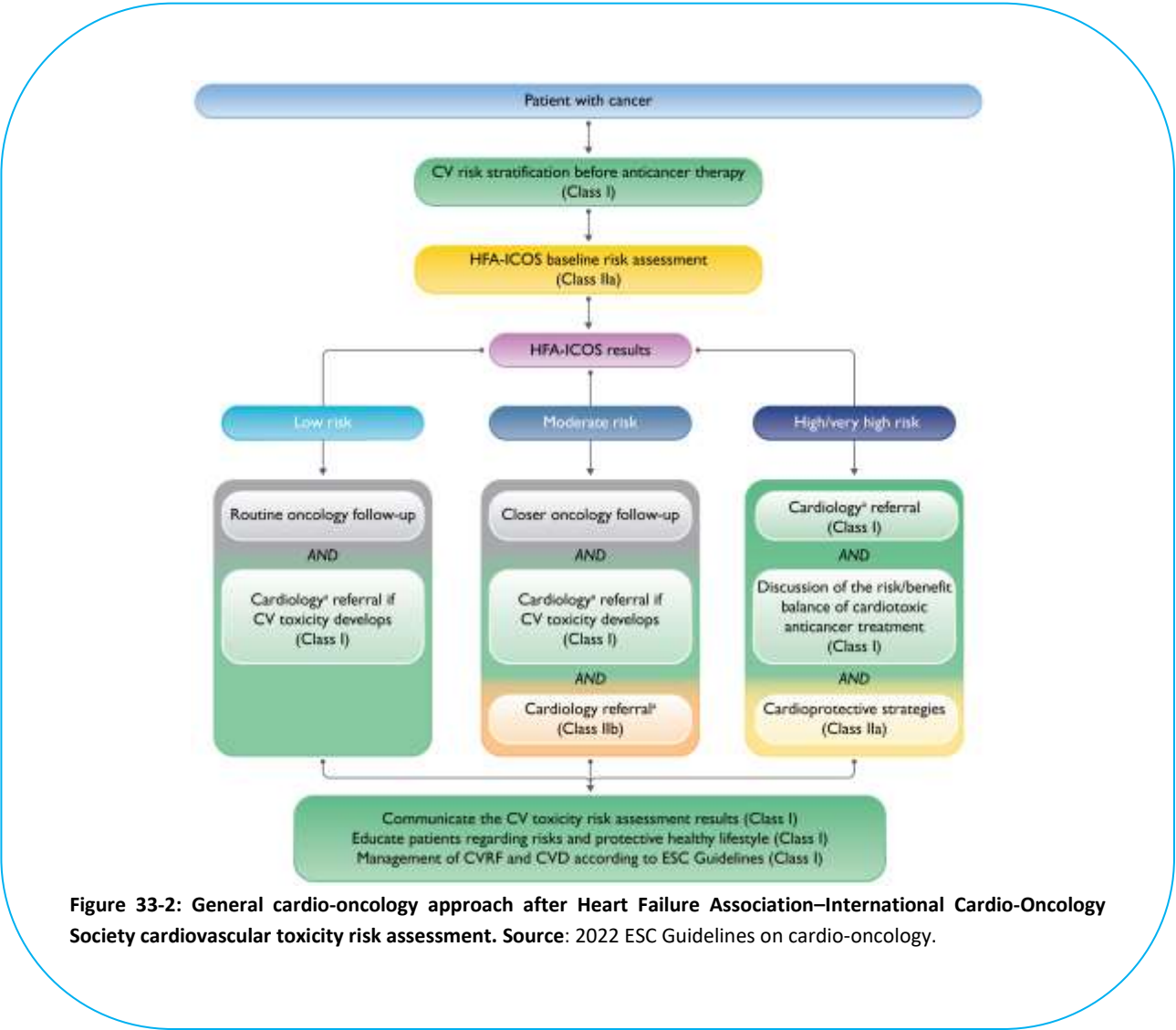


Figure 33-2: General cardio-oncology approach after Heart Failure Association–International Cardio-Oncology Society cardiovascular toxicity risk assessment. Source: 2022 ESC Guidelines on cardio-oncology.

Table 33-3: ESC Recommendations for general approach to CV toxicity risk categorization:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>CV toxicity risk stratification ⁽¹⁾ before starting potentially cardiotoxic anticancer therapy is recommended in all patients with cancer.</i> | I | B |
| <i>Cardiology referral is recommended for patients with cancer and pre-existing CVD or abnormal findings at baseline CV toxicity risk assessment ⁽²⁾ who require potentially cardiotoxic anticancer therapy.</i> | I | C |
| <i>The use of HFA-ICOS risk assessment should be considered to stratify CV toxicity risk in patients with cancer scheduled to receive cardiotoxic anticancer therapy.</i> | IIa | C |
| <i>It is recommended that patients categorized to be at low CV toxicity risk should proceed to anticancer therapy without delay.</i> | I | C |
| <i>In patients categorized at moderate CV toxicity risk, cardiology referral may be considered Without delaying cancer treatments.</i> | IIb | C |
| <i>Cardiology referrals is recommended in high-risk and very high-risk patients before anticancer therapy Unless there is an oncology emergency requiring immediate cancer treatment.</i> | I | C |
| <i>Discussion of the risk/benefit balance of cardiotoxic anticancer treatment in high- and very high-risk patients in a multidisciplinary approach prior to starting treatment is recommended.</i> | I | C |

Prevention of CV complications during cancer therapy:

Table 33-4: ESC Recommendations for primary prevention of CTR-CVT:

| Recommendations | Class | Level |
|------------------------|--------------|--------------|
|------------------------|--------------|--------------|

- (1) Including clinical history and physical examination, ECG, general blood test, HbA1c, lipid profile, and cardiac serum biomarkers and/or TTE (according to cancer drug type and CV toxicity risk).
- (2) Moderate-to-severe pre-existing CVDs or new abnormal findings (baseline cardiac biomarkers > ULN, LVEF ≤ 50%, GLS under normal local values, previously undiagnosed moderate-to-severe myocardial, pericardial, or VHDs, abnormal baseline ECG).

| | | |
|---|------------|----------|
| <i>Management of CVRF according to the Guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy Without delaying cancer treatments.</i> | I | C |
| <i>Dexrazoxane ⁽¹⁾ should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.</i> | IIa | B |
| <i>Liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.</i> | IIa | B |
| <i>ACE-I or ARB and beta-blockers ⁽²⁾ recommended for HF should be considered for primary prevention in high- and very high-risk patients receiving anthracyclines, anti-HER2 therapies or targeted cancer therapies that may cause HF ⁽³⁾.</i> | IIa | B |
| <i>Statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk.</i> | IIa | B |

Monitoring of CV complications during cancer therapy:

• CV complications of chemotherapy:

-
- (1)** Dexrazoxane is an iron chelator that binds free iron or removes iron from the doxorubicin-iron complex, thereby preventing oxygen free radical formation. The FDA has designated dexrazoxane as an orphan drug for use in the prevention or reduction in the incidence and severity of anthracycline-induced cardiomyopathy. The common side effects include dose-limiting myelotoxicity (neutropenia, leukopenia, and thrombocytopenia), which is very similar to the side-effect profile of anthracyclines. It is, therefore, challenging to distinguish the adverse effects seen with dexrazoxane use from those of anthracycline chemotherapy.
- (2)** Carvedilol (preferred beta-blocker for CV protection if there is no contraindication), bisoprolol, controlled/extended-release metoprolol succinate and nebivolol.
- (3)** VEGFi and bevacizumab, RAF inhibitor, MEK inhibitor, PI, dasatinib, ponatinib, and osimertinib.

| |  Arrhythmia |  Cardio-myopathy |  Arterial vascular disease |  Venous thrombo-embolism |  Pulmonary hypertension |  Systemic hypertension |  Pericardial disease |  Valvular heart disease |
|--|--|--|---|---|--|---|---|--|
| Conventional chemotherapies | | | | | | | | |
| Anthracyclines (doxorubicin, epirubicin) | | ✓ | | | | | | |
| Alkylating agents (cyclophosphamide, melphalan) | ✓ | ✓ | ✓ | | | | | |
| Antimetabolites (5-fluorouracil, capecitabine, cytarabine) | | ✓ | ✓ | | | | ✓ Cytarabine | |
| Microtubule-binding agents (paclitaxel) | ✓ | | ✓ | | | | | |
| Platinum-based therapy (cisplatin) | | | ✓ | ✓ | | ✓ | | |
| Antibiotic (bleomycin) | | | ✓ | | ✓ | | | |
| Immunomodulatory drugs (thalidomide) | ✓ | | | ✓ | | | | |
| Targeted agents | | | | | | | | |
| Proteasome inhibitors (bortezomib, carfilzomib) | | ✓ | ✓ | | | ✓ | | |
| HDAC inhibitors (vorinostat) | ✓ | | | | | | | |
| CDK4/CDK6 inhibitors (ribociclib) | ✓ | | | | | | | |
| mTOR inhibitors (everolimus) | ✓ | ✓ | ✓ | ✓ | | ✓ | | |
| HER2 inhibitors (pertuzumab, trastuzumab) | | ✓ | | | | | | |
| VEGF inhibitors (bevacizumab, sunitinib) | | ✓ | ✓ | ✓ | | ✓ | | |
| BCR-ABL1 inhibitors (dasatinib, nilotinib, ponatinib) | ✓ | | ✓ | ✓ | ✓ Dasatinib | | | |
| BTK inhibitors (ibrutinib) | ✓ | | | | | | | |
| ALK inhibitors (alectinib, ceritinib, crizotinib) | ✓ | | | | ✓ | | | |
| BRAF inhibitors (dabrafenib) | ✓ | ✓ | | | | | | |
| MEK inhibitors (binimetinib, cobimetinib, trametinib) | ✓ | ✓ | | | ✓ | | | |
| Immunotherapies | | | | | | | | |
| Immune checkpoint inhibitors | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | |
| CAR T cell therapy | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | |
| Other therapies | | | | | | | | |
| Radiation therapy | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ |

Figure 33-3: Outline of cardiovascular toxic effects associated with cancer therapies. Source: Herrmann, J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol* 17, 474–502 (2020).

- **Diagnostic tools for monitoring of CTR-CVT:**

- A careful clinical evaluation and physical examination is recommended during cancer treatment.
- ECG monitoring is required in patients at risk of cardiac arrhythmias according to specific drug protocols.
- NP and cTn should be used for CTRCD screening and diagnosis and they may also serve to guide therapy.
- Cardiac imaging plays a critical role in clinical decision-making during the cancer process. The same imaging modality is recommended throughout the entire treatment to decrease inter-technique variability. Cardiac imaging should be performed at any time if patients present with new cardiac symptoms. Currently, a relative GLS decrease of > 15% compared with baseline is the recommended threshold to predict future LVEF reduction.

• **CTR-CVT monitoring protocols:**

| Table 33-5: ESC Recommendations for CTR-CVT monitoring protocols: | | | | | | | | |
|---|------------------|-------------|---------------|----------|---------------|-------------------------------|-------------------------|----------------------------|
| Baseline | | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | 3 months after therapy |
| Anthracycline: | | | | | | | | |
| Moderate risk | ECG, TTE, CTn/NP | | CTn/NP | | TTE, CTn/NP | | CTn/NP | CTn/NP |
| High & very high risk | | CTn/NP | TTE CTn/NP | CTn/NP | TTE CTn/NP | CTn/NP | TTE CTn/NP | TTE CTn/NP |
| Baseline | | 3 months | 6 months | 9 months | 12 months | 3 months after therapy | 12 months after therapy | Every year |
| Human epidermal receptor 2 (HER2)-targeted therapy: | | | | | | | | |
| Low and moderate risk | ECG, TTE | TTE | | | | | TTE | |
| High & very high risk | ECG, TTE, CTn/NP | TTE, cTn/NP | | | | | | |
| Vascular endothelial growth factor inhibitors (VEGFI): | | | | | | | | |
| Moderate risk | ECG TTE | | | | | | | TTE |
| High & very high risk | ECG, TTE, NP | TTE, NP | | | | | | TTE |
| Hematopoietic Stem cell transplantation: | | | | | | | | |
| Low risk | CV assessment | | | | | CV assessment ECG | | |
| High risk | ECG, TTE, NP | | | | | CV assessment ECG, TTE, NP | | CV assessment ECG NP |

Management of CV toxicity in patients receiving cancer therapy:

- **Cancer therapy-related cardiac dysfunction:**
 - Anthracycline chemotherapy-related cardiac dysfunction:

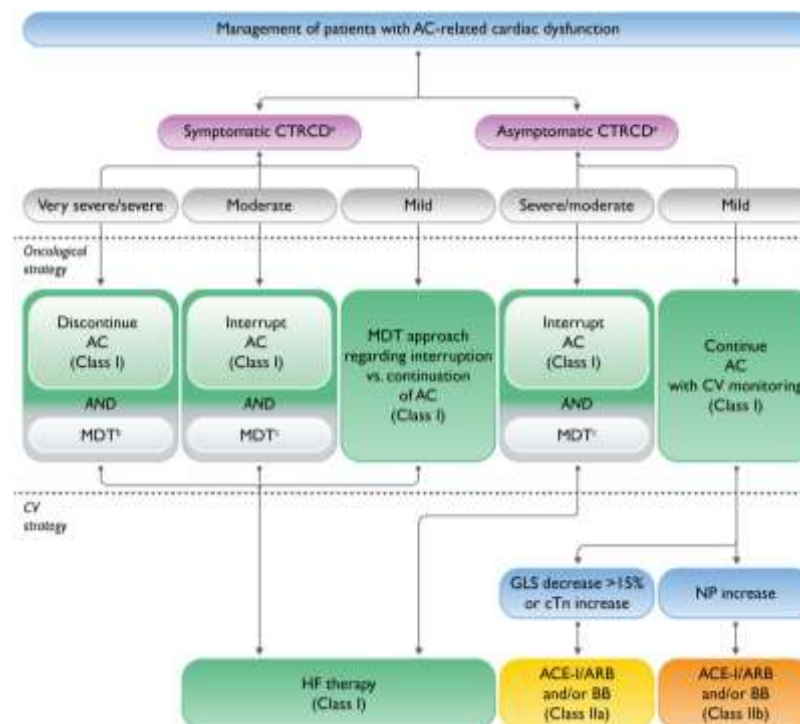


Figure 33-4: Management of anthracycline chemotherapy-related cardiac dysfunction. (A) Symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF < 40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF > 50%). (B) In rare exceptions, anthracycline chemotherapy may be restarted after recovery of LV function with optimal HF therapy. (C) A MDT discussion is recommended before restarting anthracycline chemotherapy after recovery of LV function. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-6: ESC Recommendations for the management of cancer treatment-related cardiac dysfunction during anthracycline chemotherapy:

| Recommendations | Class | Level |
|---|--------------|--------------|
| Anthracycline chemotherapy-induced symptomatic CTRCD: | | |
| <i>HF therapy is recommended for patients who develop symptomatic CTRCD during anthracycline chemotherapy.</i> | I | B |
| <i>Discontinuation of anthracycline chemotherapy is recommended in patients who develop symptomatic severe CTRCD ⁽¹⁾.</i> | I | C |
| <i>Temporary interruption of anthracycline chemotherapy is recommended in patients who develop symptomatic moderate CTRCD and a multidisciplinary approach regarding the decision to restart is recommended.</i> | I | C |
| <i>A multidisciplinary approach regarding interruption vs. continuation of anthracycline chemotherapy is recommended in patients who develop mild symptomatic CTRCD.</i> | I | C |
| Anthracycline chemotherapy-induced asymptomatic CTRCD: | | |
| <i>Temporary interruption of anthracycline chemotherapy and initiation of HF therapy is recommended in patients who develop asymptomatic moderate or severe CTRCD.</i> | I | C |
| <i>A multidisciplinary approach regarding the decision when to restart is recommended in all patients with moderate or severe asymptomatic CTRCD.</i> | I | C |
| <i>Continuation of anthracycline chemotherapy is recommended in asymptomatic patients who have LVEF \geq 50% and who have developed a significant fall in GLS or a troponin or a NP elevation $>$ ULN.</i> | I | C |
| <i>Asymptomatic patients who have LVEF \geq 50% and who have developed a significant fall in GLS should be considered for ACE-I/ARB and/or beta-blockers.</i> | IIa | B |

(1) Significant fall in GLS = relative reduction $>$ 15%.

| | | |
|--|------------|----------|
| <i>Asymptomatic patients who have LVEF \geq 50% and who have developed a troponin elevation $>$ ULN should be considered for ACE-I/ARB and/ or beta-blockers.</i> | IIa | B |
| <i>Asymptomatic patients who have LVEF \geq 50% and who have developed NP $>$ ULN may be considered for ACE-I/ARB and/or beta-blockers.</i> | IIb | C |
| Strategies for restarting anthracycline chemotherapy in patients with CTRCD: | | |
| <i>Liposomal anthracycline may be considered in patients with moderate or severe symptomatic or asymptomatic CTRCD who require further anthracycline chemotherapy to reduce the risk of further CV toxicity.</i> | IIb | C |
| <i>Dexrazoxane may be considered in patients with moderate or severe symptomatic or asymptomatic CTRCD who require further anthracycline chemotherapy to reduce the risk of further CV toxicity.</i> | IIb | C |

○ Human epidermal receptor 2-targeted therapy-related cardiac dysfunction:

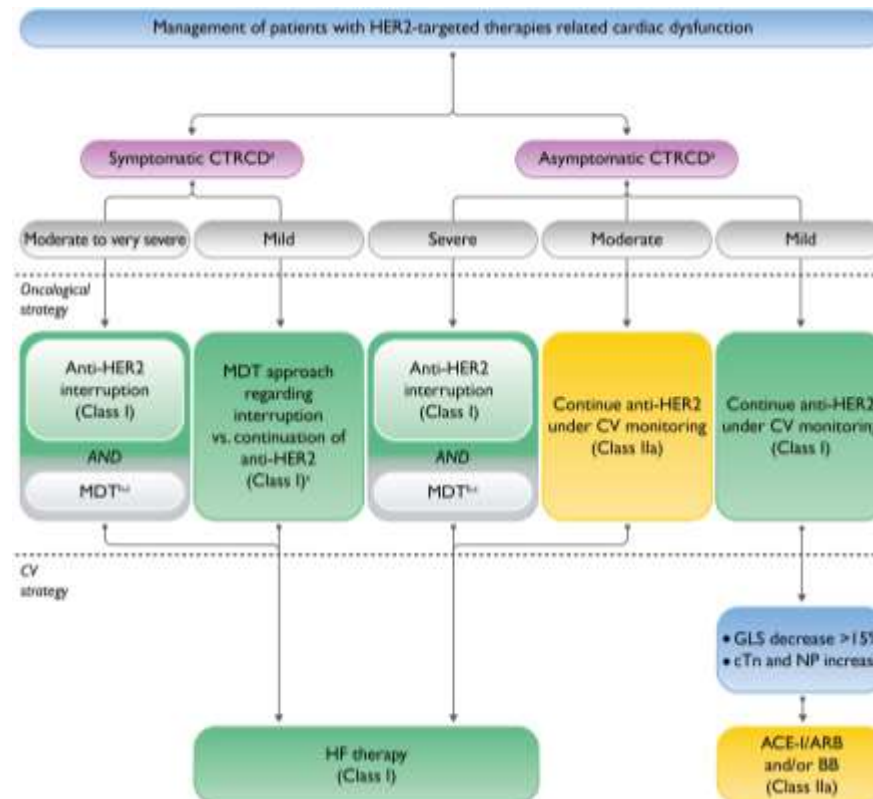


Figure 33-5: Management of human epidermal receptor 2-targeted therapy-related cardiac dysfunction. (A) symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF < 40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF > 50%). (B) For patients in whom HER2-targeted therapy has been interrupted, whose signs and symptoms of HF do not resolve and/or LVEF remains < 40%, resumption of HER2-targeted therapy may be considered if no alternative therapeutic option exists. In advanced cancer that only responds well to trastuzumab, the risk/benefit ratio may warrant continued therapy if other options remain limited. (C) For patients where HER2-targeted therapy has been interrupted and who have recovered LVEF ≥ 40% and are now asymptomatic, resumption of HER2-targeted therapy should be considered, supported by HF therapy, and echocardiography and cardiac biomarker assessment every two cycles for the first four cycles after restarting and then the frequency can be reduced. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-7: ESC Recommendations for the management of CTRCD during HER2-targeted therapies:

| Recommendations | Class | Level |
|--|--------------|--------------|
| HER2-targeted therapy-induced symptomatic CTRCD: | | |
| <i>HF therapy is recommended for patients who develop symptomatic moderate-to-severe CTRCD with LVEF < 50% during HER2-targeted treatment.</i> | I | B |
| <i>Temporary interruption of HER2-targeted treatment is recommended in patients who develop moderate or severe symptomatic CTRCD and the decision to restart should be based on a multidisciplinary approach after improvement of LV function and symptoms resolved.</i> | I | C |
| <i>In patients who develop mild symptomatic CTRCD, HF therapy and a multidisciplinary approach regarding the decision to continue vs. interrupt HER2-targeted therapy are recommended.</i> | I | C |
| HER2-targeted therapy-induced asymptomatic CTRCD | | |
| <i>Temporary interruption of HER2-targeted therapy and initiation of HF therapy is recommended in patients who develop asymptomatic severe CTRCD.</i> | I | C |
| <i>A multidisciplinary approach regarding the decision to restart HER2-targeted treatment is recommended in patients with severe asymptomatic CTRCD.</i> | I | C |
| <i>Continuation of HER2-targeted therapy should be considered in patients who develop asymptomatic moderate (LVEF 40–49%) CTRCD with more frequent cardiac monitoring.</i> | IIa | B |
| <i>Continuation of HER2-targeted therapy is recommended in patients who develop asymptomatic mild (LVEF ≥ 50%) CTRCD with more frequent cardiac monitoring.</i> | I | C |
| <i>ACE-I/ARB and beta-blockers are recommended in patients who develop asymptomatic moderate (LVEF 40–49%) CTRCD during HER2-targeted treatment.</i> | I | C |

| | | |
|---|------------|----------|
| <i>ACE-I/ARB and/or beta-blockers should be considered in asymptomatic patients receiving HER2-targeted therapies who have LVEF \geq 50% but develop a significant fall in GLS while continuing HER2-targeted therapy.</i> | Ila | B |
| <i>ACE-I/ARB and/or beta-blockers should be considered in asymptomatic patients receiving HER2-targeted therapies who have LVEF \geq 50% but develop a new troponin or NP rise while continuing HER2-targeted therapy.</i> | Ila | B |

○ **Immune checkpoint inhibitor (ICI)-associated myocarditis:**

Myocarditis is a severe complication of ICI with a high fatality rate that most frequently develops during the first 12 weeks of treatment, although late cases (after week 20) may occur. The diagnosis of ICI-associated myocarditis is initially based on the presence of symptoms, a new increase in troponin (associated with either CV symptoms or non-CV immuno-related adverse events), and new ECG abnormalities (AV or intraventricular conduction disorders, bradycardia, tachyarrhythmias). All cases of ICI-associated myocarditis should be classified according to the severity of the myocarditis to guide the management pathway.

| Table 33-8: ESC Recommendations for the diagnosis and management of ICI-associated myocarditis: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>cTn, ECG, and CV imaging (echocardiography and CMR) are recommended to diagnose ICI-associated myocarditis.</i> | I | B |
| <i>In patients with suspected ICI-associated myocarditis, temporary interruption of ICI treatment is recommended until the diagnosis is confirmed or refuted.</i> | I | C |
| <i>EMB should be considered to confirm the diagnosis of ICI-associated myocarditis if the diagnosis is suspected but not confirmed after cardiac imaging and biomarkers.</i> | Ila | C |
| <i>Interruption of ICI treatment is recommended in patients with confirmed ICI-associated myocarditis.</i> | I | C |
| <i>Continuous ECG monitoring to assess for new AV block and tachyarrhythmias during the acute phase is recommended for all patients with symptomatic ICI-associated myocarditis.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Early high-dose corticosteroids ⁽¹⁾ are recommended in patients with cancer and confirmed ICI-associated myocarditis.</i> | I | C |
| <i>Continuation of high-dose corticosteroids is recommended for the treatment of ICI-associated myocarditis until resolution of symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction ⁽²⁾.</i> | I | C |
| <i>Switching from i.v. to oral prednisolone should be considered after clinical improvement (resolution of: symptoms, LV systolic dysfunction, conduction abnormalities, and significant cTn reduction) ⁽³⁾.</i> | IIa | C |
| <i>Second-line immunosuppression treatment should be considered in patients with steroid-refractory ICI-associated myocarditis ⁽⁴⁾.</i> | IIa | C |
| <i>Admission to ICU (level 3), treatment with i.v. methylprednisolone, and optimal CV treatment including mechanical support (when indicated) is recommended for patients with ICI-associated fulminant myocarditis.</i> | I | C |
| <i>A single dose of i.v. methylprednisolone should be considered in unstable ⁽⁵⁾ patients with cancer where ICI-induced myocarditis is suspected.</i> | IIa | C |
| <i>A multidisciplinary discussion is recommended before restarting ICI treatment in selected patients with previous uncomplicated ICI-associated myocarditis.</i> | I | C |

(1) Early: ≤ 24 h; high-dose corticosteroids (methylprednisolone 500–1000 mg/day).

(2) Reduction of cTn by > 50% from peak level.

(3) Complete recovery: Patients with complete resolution of acute symptoms, normalization of biomarkers, or reduction of cTn by > 50% from peak level and recovery of LVEF after discontinuation of immunosuppression are considered to have achieved complete recovery. CMR may still show LGE or elevated T1 due to fibrosis but any suggestion of acute oedema should be absent. Incomplete recovery: (1) an increase in symptoms or biomarkers of myocarditis or an inability to taper immunosuppression without a clinical or biomarker flare; (2) patients with persistent LVD despite resolution of acute symptoms with immunosuppression.

(4) Steroid refractory: non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone

(5) Unstable: patients with symptomatic HF, ventricular arrhythmias, new complete heart block.

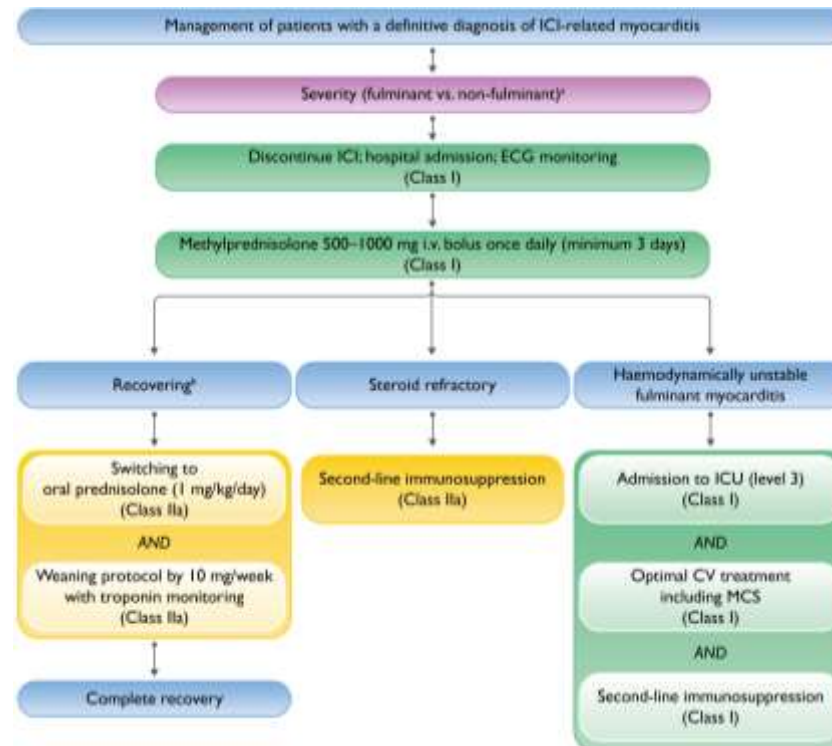


Figure 33-6: Diagnosis and management of immune checkpoint inhibitor-related myocarditis. A) Fulminant: haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia. **Non-fulminant:** including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease. **B) Recovering:** ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression. **Complete recovery:** patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute oedema should be absent. **Source:** 2022 ESC Guidelines on cardio-oncology

- **Chimeric antigen receptor T cell (CAR-T) and tumour-infiltrating lymphocytes therapies and heart dysfunction:** The most common CV complications in patients receiving CAR-T therapies are arrhythmias (including QTc prolongation, ventricular arrhythmias, and AF); HF; and MI and VTE.
When suspected, a resting 12-lead ECG, continuous ECG monitoring, TTE, and cTn and NP are recommended. Admission to ICU is recommended in severe cases due to the risk of malignant cardiac arrhythmias, circulatory collapse, and multiorgan system failure.
- **HF during haematopoietic stem cell transplantation (HSCT):** CV complications during HSCT, including congestive HF, arterial events, tamponade, and rhythm disturbances (AF, atrial flutter, and supraventricular tachycardia), are uncommon but clinically relevant.
- **Takotsubo syndrome and cancer:**

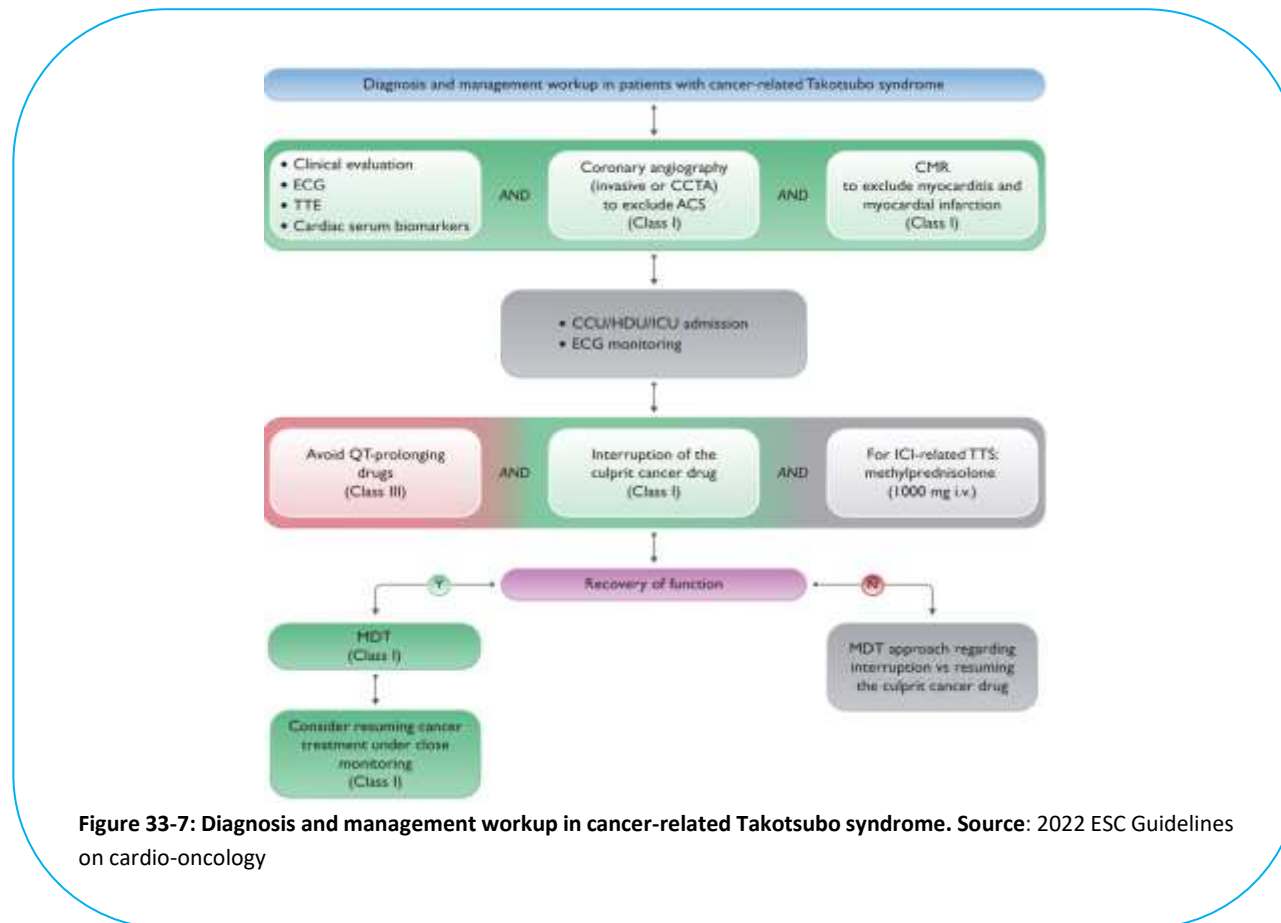


Table 33-9: ESC Recommendations for the diagnosis and management of Takotsubo syndrome in patients with cancer:

| Recommendations | Class | Level |
|--|-------|-------|
| Coronary angiography (invasive or CCTA) is recommended to exclude ACS. | I | C |
| CMR is recommended to exclude myocarditis and MI. | I | B |
| QT-prolonging drugs are not recommended during the acute Takotsubo syndrome phase. | III | C |

▪ **Coronary artery disease:**

Patients with cancer are at increased risk of CAD because of shared CVRFs and CV toxicity of cancer therapy compounded by a cancer-induced pro-inflammatory and prothrombotic state.

Table 33-10: ESC Recommendations for the management of acute coronary syndromes in patients receiving anticancer treatment:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Acute Coronary Syndromes: | | |
| <i>An invasive strategy is recommended in patients with cancer presenting with STEMI or high-risk NSTEMI-ACS with life expectancy ≥ 6 months.</i> | I | B |
| <i>A conservative non-invasive strategy should be considered in patients with poor cancer prognosis (with life expectancy < 6 months) and/or very high bleeding risk presenting with STEMI or NSTEMI-ACS</i> | IIa | C |
| <i>A temporary interruption of cancer therapy is recommended in patients where the cancer therapy is suspected as a contributing cause.</i> | I | C |
| <i>A short DAPT strategy should be considered in patients with cancer with very high bleeding risk treated with PCI for an ACS.</i> | IIa | C |
| <i>In patients with cancer, thrombocytopenia, and ACS, aspirin is not recommended if platelets $< 10\ 000/\mu\text{L}$.</i> | III | C |
| <i>In patients with cancer, thrombocytopenia, and ACS, clopidogrel is not recommended if platelets $< 30\ 000/\mu\text{L}$ and prasugrel or ticagrelor are not recommended if platelets $< 50\ 000/\mu\text{L}$.</i> | III | C |
| <i>Ticagrelor or prasugrel may be considered in patients with cancer with low bleeding risk and excessive thrombotic risk who are treated with PCI for ACS.</i> | IIb | C |
| Chronic coronary syndromes: | | |

Individualized duration of DAPT is recommended in patients with cancer with CCS, following revascularization, based upon thrombotic/ischemic and bleeding risk, type and stage of cancer, and current cancer treatment.

I C

▪ **Valvular heart disease:**

New or worsening VHD in patients with cancer may be related to coexisting conditions, including CTRCD, ACS, PH, endocarditis, cardiac tumors, and mechanical prosthetic valve thrombosis.

Pre-existing severe VHD is associated with an increased risk of CTRCD, and may also pose a risk for cancer surgery outcomes.

▪ **Cardiac arrhythmias:**

○ **Atrial fibrillation:**

- All types of cancer show increased risk of AF, but the risk of AF depends on the cancer type and stage.
- AF during a cancer treatment may be caused by a specific therapy or interaction with a pre-existing substrate in older patients with cancer.
- In patients with cancer, the occurrence of AF is associated with a two-fold higher risk of systemic thromboembolism/stroke and a six-fold increase in the risk of HF.
- The coexistence of cancer increases the risk of all-cause mortality, major bleeding, and intracranial hemorrhage in patients with AF.
- The management of AF in patients with cancer should follow the ESC Guidelines for the diagnosis and management of atrial fibrillation and the 'ABC pathway'.
- A complex issue in patients with cancer with new AF is risk stratification for stroke/systemic embolism, which according to guidelines, should be based on the CHA2DS2-VASc score. For bleeding risk assessment, the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score may be considered.

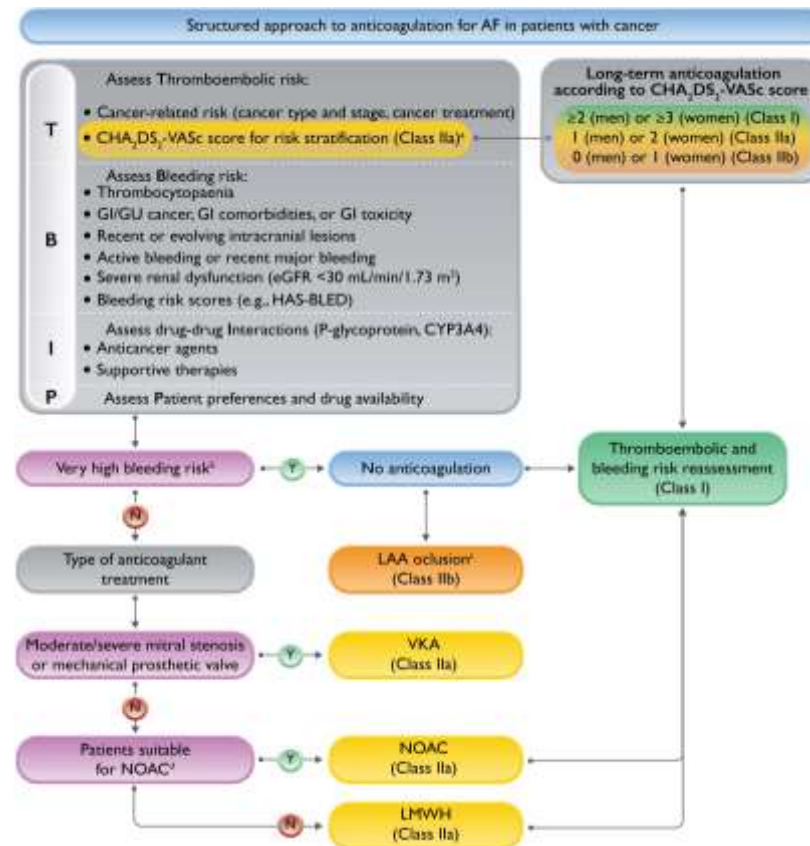


Figure 33-8: Structured approach to anticoagulation for atrial fibrillation in patients with cancer. A) In selected patients, cardiac imaging parameters related to increased thromboembolic risk should be considered (LAA thrombus, severely dilated left atrium, severely impaired LA strain). **B) Very high bleeding risk:** active or recent major bleeding (< 1 month previously); recent/evolving intracranial lesions; platelet count < 25 000/μL. According to the International Society on Thrombosis and Haemostasis, major bleeding is defined as a fall in haemoglobin level ≥ 2 g/dL and/or transfusion of ≥ 2 units of red blood cells and/or fatal bleeding and/or bleeding in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). **C)** Percutaneous left appendage closure may be considered in patients with a life expectancy of > 1 year who are at high thromboembolic and bleeding risk and in whom anticoagulation is contraindicated. **D)** Conditions favouring LMWH: unoperated GI/GU cancer; GI comorbidities or toxicity; severe renal dysfunction (CrCl < 15 mL/min); NOAC major drug–drug interactions, platelet count < 50 000/μL. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-11: ESC Recommendations for the management of AF in patients receiving anticancer treatment:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>CHA2DS2-VASc score should be considered for risk stratification for stroke/systemic thromboembolism taking into account that it may underestimate the actual thromboembolic risk.</i> | Ila | C |
| <i>Long-term anticoagulation is recommended for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA2DS2-VASc score ≥ 2 (men) or ≥ 3 (women) as per the ESC Guidelines for the diagnosis and management of atrial fibrillation.</i> | I | C |
| <i>Long-term anticoagulation should be considered for stroke/systemic thromboembolism prevention in patients with cancer with AF and a CHA2DS2-VASc score = 1 (men) or = 2 (women) as per the ESC Guidelines for the diagnosis and management of atrial fibrillation.</i> | Ila | C |
| <i>Patients with cancer ⁽¹⁾, AF, and CHA2DS2-VASc score 0 (men) or 1 (women) may have a higher thrombotic risk than patients without cancer and may be considered for therapeutic anticoagulation after consideration of the bleeding risk.</i> | Ilb | C |
| <i>Thromboembolic and bleeding risk reassessment is recommended during follow-up in patients with cancer with AF ⁽²⁾.</i> | I | C |

(1) Factors that may increase thromboembolic risk in patients with cancer including comorbidities (proteinuria > 150 mg/24 h, eGFR < 45 mL/min/1.73 m², BMI ≥ 30 kg/m², thrombophilia), cancer type (pancreatic, gastric, ovarian, brain, lung, MM), cancer stage (metastatic disease) anticancer therapies: alkylating agents, aflibercept, bevacizumab, anthracyclines, capecitabine, 5-FU, gemcitabine, methotrexate, EGFR inhibitors, bleomycin, axitinib, lenvatinib, pazopanib, sorafenib, sunitinib, carfilzomib, irinotecan, taxanes, tasonermin, tretinoin.

(2) Stroke and bleeding risk may change during both cancer treatment and the course of the underlying disease; reassessment is important to inform treatment decisions and address potentially modifiable bleeding risk factors.

| | | |
|---|------------|----------|
| <i>NOAC should be considered for stroke prevention in preference to LMWH and VKA (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) in patients without a high bleeding risk, significant drug-drug interactions, or severe renal dysfunction.</i> | Ila | B |
| <i>LMWH should be considered in patients with active cancer ⁽¹⁾ and AF who are not suitable for NOAC ⁽²⁾.</i> | Ila | C |
| <i>LAA occlusion may be considered for stroke prevention in patients with cancer with AF and contraindications for long-term anticoagulation with a life expectancy > 12 months.</i> | Ilb | C |
| <i>Antiplatelet therapy or prophylactic LMWH are not recommended for stroke or systemic thromboembolism prevention in AF with cancer.</i> | III | C |
| <i>Heart rate control strategy, preferably with beta-blockers, should be considered in patients who develop well-tolerated AF while they are receiving active cancer treatment ⁽³⁾.</i> | Ila | C |

○ **Long QTc interval and ventricular arrhythmias:**

VA are not common during cancer, although their incidence increases with advanced cancer and CV comorbidities.

Most cancer therapy-induced VA are related to a prolongation of QTc leading to the development of TdP. In patients with cancer, the Fridericia formula is recommended and has demonstrated less error than other correction methods.

The administration of class IA, IC, and III anti-arrhythmic drugs is limited by the risk of drug-drug interactions and QTc prolongation. Beta-blockers and class IB drugs are less likely to cause drug interactions or QTc prolongation. Amiodarone is the antiarrhythmic drug of choice in patients with structural heart disease and hemodynamic instability.

(1) Patients receiving cancer treatment, patients diagnosed with cancer in the past 6 months, and patients with progressive or advanced disease.

(2) High bleeding risk, severe renal dysfunction (CrCl < 15 mL/min); NOAC major drug–drug interactions.

(3) Asymptomatic or mild symptomatic patients without HF signs or symptoms or deterioration of LV function. The optimal heart rate target in AF patients is unclear. A resting heart rate < 110 bpm (i.e., lenient rate control) should be considered as the initial heart rate target for rate control therapy. A review of rate vs. rhythm strategy should be made at the end of cancer treatment.

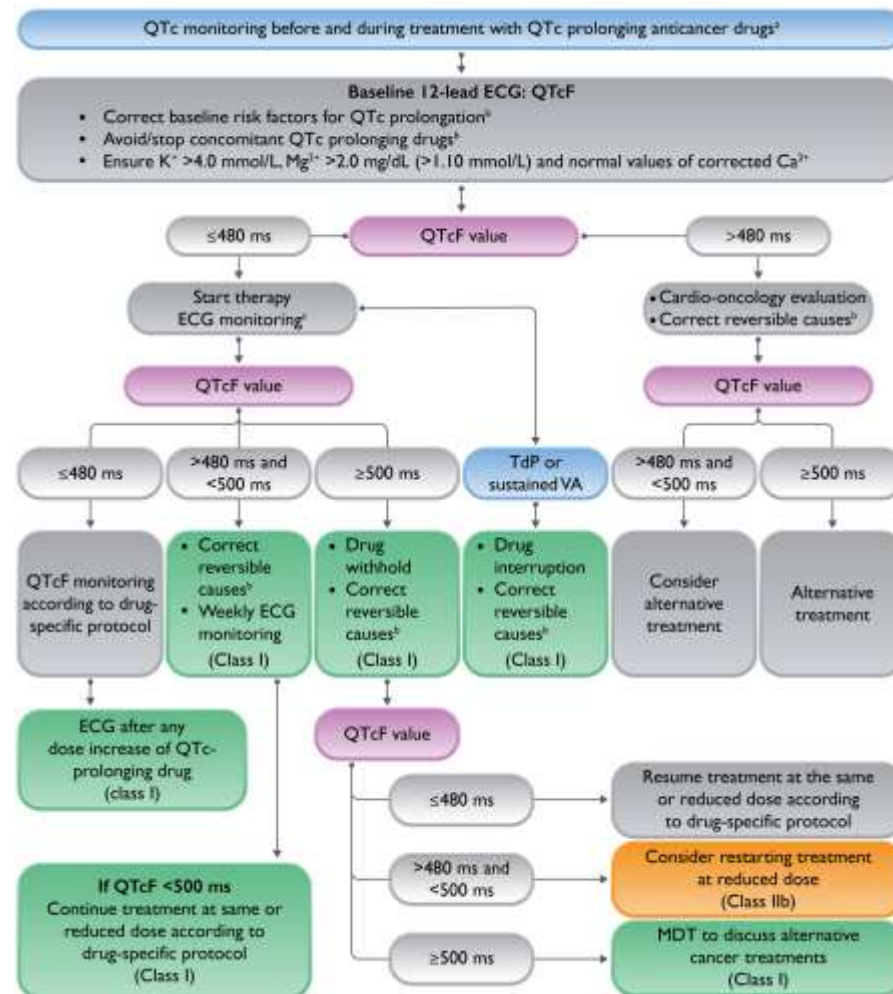


Figure 33-9: Corrected QT interval monitoring before and during treatment with corrected QT interval-prolonging anticancer drugs. QT interval using Fridericia correction (QTcF = QT/√RR) is recommended in patients with cancer. Upper 99% limits of normal for QTc values in the general population are 450 ms for men and 460 ms for women. **C)** ECG monitoring at baseline, once steady-state anticancer drug levels have been achieved, after each dose modification, or any treatment interruption > 2 weeks; monthly for the first 3 months, and then periodically during treatment depending on patient-specific risk factors and cancer treatment. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-12: ESC Recommendations for the management of long corrected QT interval and ventricular arrhythmias in patients receiving anticancer treatment:

| Recommendations | Class | Level |
|--|--------------|--------------|
| How to manage QTc prolongation in patients with cancer: | | |
| <i>Discontinuation of QTc-prolonging cancer therapy is recommended in patients who develop TdP or sustained ventricular tachyarrhythmias during treatment.</i> | I | C |
| <i>Temporary interruption of QTc-prolonging cancer therapy is recommended in patients who develop asymptomatic QTcF ≥ 500 ms and an ECG should be repeated every 24 h until resolution of the QTcF prolongation.</i> | I | C |
| <i>Immediate withdrawal of any offending drug and correction of electrolyte abnormalities and other risk factors^c is recommended in patients with cancer who develop QTcF ≥ 500 ms.</i> | I | C |
| <i>Weekly ECG monitoring is recommended in asymptomatic patients with cancer with QTcF 480–500 ms who are treated with a QTc-prolonging cancer therapy.</i> | I | C |
| <i>A 12-lead ECG is recommended after any dose increase of QTc-prolonging cancer therapy.</i> | I | C |
| Restarting QTc-prolonging cancer therapy: | | |
| <i>A multidisciplinary discussion is recommended before restarting QTc-prolonging drugs in patients who have developed significant QTcF prolongation, to discuss alternative cancer treatments.</i> | I | C |
| <i>In patients who experienced significant QTcF prolongation, restarting the culprit QTc-prolonging cancer treatment may be considered, ideally at a reduced dose according to each drug recommendation.</i> | IIb | C |
| <i>Weekly ECG monitoring during the first 4–6 weeks and then monthly thereafter is recommended in patients with cancer after restarting QTc-prolonging cancer therapy.</i> | I | C |

▪ **Arterial hypertension:**

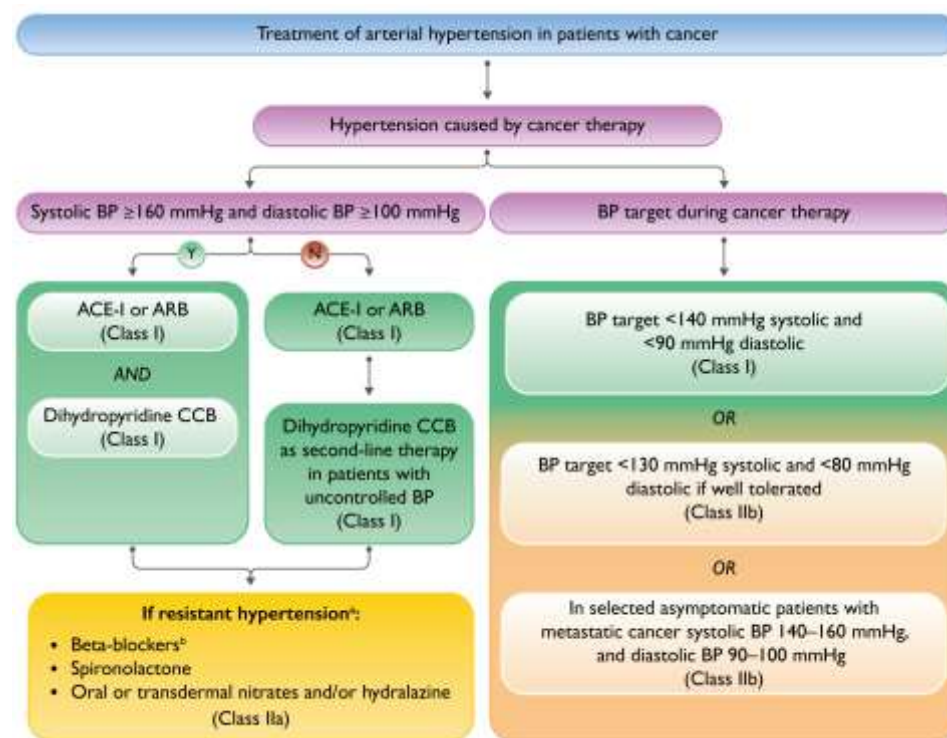


Figure 33-10: Treatment of arterial hypertension in patients with cancer. Treatment of hypertension with ACE-I or ARB as first-line therapy is recommended to reduce the risk of CTRCD. Combination therapy with an ACE-I or ARB and a dihydropyridine CCB is recommended due to the more rapid onset of BP control with the combination compared with ACE-I/ARB monotherapy. **A)** Resistant hypertension is defined as BP being uncontrolled despite treatment with optimal or best-tolerated doses of three or more drugs including a diuretic, and confirmed by ambulatory and home BP monitoring. **B)** Consider beta-blockers (nebivolol or carvedilol are preferred in patients on VEGFi) at any treatment step, when there is a specific indication for their use, e.g., HF, angina, post-MI, or AF. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-13: ESC Recommendations for the management of arterial hypertension in patients receiving anticancer treatment:

| Recommendations | Class | Level |
|--|--------------|--------------|
| General: | | |
| <i>Effective treatment of cancer therapy-induced arterial hypertension to prevent cancer treatment interruption and CV complications is recommended.</i> | I | C |
| <i>A BP target < 140 mmHg systolic and < 90 mmHg diastolic is recommended during cancer therapy.</i> | I | C |
| <i>A BP target < 130 mmHg systolic and < 80 mmHg diastolic may be considered during cancer therapy provided that the treatment is well tolerated.</i> | IIb | C |
| <i>In selected asymptomatic patients with metastatic cancer, a systolic BP 140–160 mmHg and diastolic BP 90–100 mmHg treatment threshold may be considered provided there is ongoing BP monitoring.</i> | IIb | C |
| <i>The competing cancer and CV risk evaluation is recommended if the systolic BP is \geq 180 mmHg or diastolic BP \geq 110 mmHg, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values < 160 mmHg (systolic) and < 100 mmHg (diastolic).</i> | I | C |
| Cancer therapy-induced arterial hypertension treatment: | | |
| <i>ACE-I or ARB are the first-line antihypertensive drugs recommended for BP management in patients with cancer.</i> | I | B |
| <i>Dihydropyridine CCB are recommended as second-line antihypertensive drugs for patients with cancer with uncontrolled BP.</i> | I | C |
| <i>Combination therapy with ACE-I or ARB and dihydropyridine CCB is recommended in patients with cancer with systolic BP \geq 160 mmHg and diastolic BP \geq 100 mmHg.</i> | I | C |

Diltiazem and verapamil are not recommended to treat arterial hypertension in patients with cancer due to their drug–drug interactions ⁽¹⁾.

III

C

■ **Thrombosis and thromboembolic Events:**

VTE, including DVT and PE, is the second-leading cause of death in patients with malignancies. Unprovoked VTE may be the first clinical sign of a malignancy, followed by a 5% incidence of cancer diagnosis during the subsequent 12 months.

Table 33-14: Risk factors for VTE in patients with cancer

| Patient-related factors | Cancer-related factors | Treatment-related factors |
|---|--|--|
| <ul style="list-style-type: none"> ○ Ageing ○ Comorbidities [Acute infection, chronic kidney disease (CrCl < 45 mL/min), pulmonary disease, obesity (BMI ≥ 30 kg/m²), ATE]. ○ Sex (female) ○ Hereditary coagulation defects (Factor V Leiden, prothrombin gene mutation) ○ Performance status ○ Prior VTE history | <ul style="list-style-type: none"> ○ Cancer type ⁽²⁾. ○ Genetic characteristics (JAK2 or K-ras mutations) Histology (adenocarcinoma) ○ Initial period after diagnosis ○ Primary site (pancreas, stomach, ovaries, brain, lung, myeloma) ○ Stage (advanced, metastatic) | <ul style="list-style-type: none"> ○ Cancer therapy ○ Central venous catheters ○ Hospitalization ○ Major surgery |

(1) *In selected patients with cancer, who are intolerant to multiple other antihypertensive drugs, diltiazem and verapamil may be considered with close monitoring of drug–drug interactions.*

(2) *Chemotherapy (carboplatin, cyclophosphamide, anthracyclines, antimetabolites, irinotecan, taxanes, tasonermin), anti-angiogenic agents (bevacizumab, axitinib, lenvatinib, pazopanib, sorafenib, sunitinib), IMiD (thalidomide, lenalidomide), PI (carfilzomib), hormonal therapy, erythropoiesis-stimulating agents.*

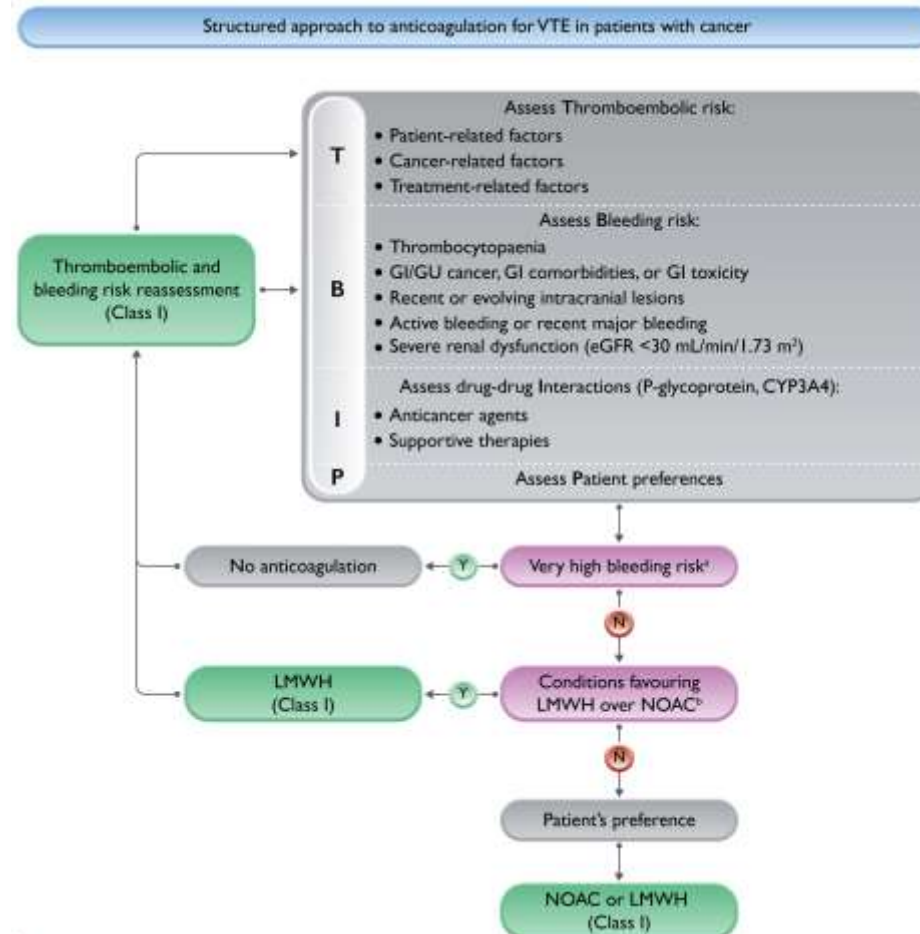


Figure 33-11: Structured approach to anticoagulation for venous thromboembolism in patients with active cancer.

A) Very high bleeding risk: active or recent major bleeding (< 1 month); recent/ evolving intracranial lesions; platelet count < 25 000/μL. According to the International Society on Thrombosis and Haemostasis, major bleeding is defined as: fall in haemoglobin level ≥ 2 g/dL, transfusion of ≥ 2 units of red blood cells, fatal bleeding, or bleeding in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). **B)** Conditions favouring LMWH: unoperated GI/GU cancer; GI comorbidities or toxicity; severe renal dysfunction (CrCl < 15 mL/min); NOAC major drug–drug interactions, platelet count < 50 000/μL. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-15: ESC Recommendations for the management and prophylaxis of venous thromboembolism in patients receiving anticancer treatment:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Apixaban, edoxaban, or rivaroxaban are recommended for the treatment of symptomatic or incidental VTE in patients with cancer without contraindications ⁽¹⁾.</i> | I | A |
| <i>LMWH are recommended for the treatment of symptomatic or incidental VTE in patients with cancer with platelet count > 50 000/μL.</i> | I | A |
| <i>In patients with cancer with platelet counts of 25 000–50 000/μL, anticoagulation with half-dose LMWH may be considered after a multidisciplinary discussion.</i> | IIb | C |
| <i>Prolongation of anticoagulation therapy beyond 6 months should be considered in selected patients with active cancer ⁽²⁾ including metastatic disease.</i> | IIa | A |
| Catheter-associated VTE | | |
| <i>Duration of anticoagulation in patients with cancer with a catheter-associated VTE is recommended for a minimum of 3 months and continuing longer if the catheter remains in situ.</i> | I | C |
| Venous thromboembolism prophylaxis: | | |
| <i>Extended prophylaxis with LMWH for 4 weeks post-operatively is recommended for patients with cancer undergoing major open or laparoscopic abdominal or pelvic surgery with low bleeding risk and high VTE risk (Reduced mobility, obesity, VTE history).</i> | I | B |

(1) High risk of GI or GU bleeding, GI absorption concerns, significant drug–drug interactions, severe renal dysfunction (CrCl < 15 mL/min), significant liver disease (ALT/AST > 2 × ULN), or significant thrombocytopenia (platelet count < 50000/μL). In addition, patients with primary brain tumors or brain metastases and acute leukemia were excluded from the seminal apixaban trial.

(2) Patients receiving cancer treatment, patients diagnosed with cancer in the past 6 months, and patients with progressive or advanced disease.

| | | |
|--|------------|----------|
| <i>Prophylactic LMWH for the primary prevention of VTE is indicated in hospitalized patients with cancer or those with prolonged bedrest or reduced mobility in the absence of bleeding or other contraindications.</i> | I | B |
| <i>For ambulatory patients with cancer at high risk of thrombosis receiving systemic therapy ⁽¹⁾, primary thromboprophylaxis with a NOAC (apixaban or rivaroxaban) or LMWH may be considered, provided there are no significant contraindications ⁽²⁾.</i> | IIb | B |
| <i>A discussion with the patient about the relative benefits and harms, cancer prognosis, drug cost, and duration of treatment is recommended prior to prophylactic anticoagulation for the primary prevention of VTE.</i> | I | C |

▪ **Bleeding complications:**

Bleeding complications are more common in patients with cancer than in patients without cancer. This may be directly related to the tumor itself, or indirectly related to chemotherapy- or RT-induced weakening of mucosal barriers.

▪ **Pulmonary hypertension:**

All five groups of the PH classification can be observed in patients with cancer.

Several cancer drugs can cause group 1 PH (pulmonary arterial hypertension [PAH]), including carfilzomib, bosutinib, dasatinib, ponatinib, interferon alpha, and alkylating agents (e.g. mitomycin C and cyclophosphamide, which mostly cause pulmonary veno-occlusive disease).

PH associated with left heart disease (group 2) is related to drugs causing HF (e.g. anthracyclines).

PH associated with lung disease (group 3) is related to drugs causing pulmonary fibrosis (e.g. bleomycin, thoracic radiation).

The most common pulmonary vascular disease complicating cancer is VTE, which can cause chronic thromboembolic PH (group 4). Of note, central venous catheters are important causes of group 4 PH complicating cancer management.

(1) Locally advanced or metastatic pancreas or lung cancer or Khorana score ≥ 2

(2) Risk factors for bleeding, significant drug–drug interactions, or severe renal dysfunction.

Table 33-16: ESC Recommendations for the management of pulmonary hypertension during anticancer treatment:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Right-heart catheterization and discontinuation of dasatinib is recommended in patients who develop symptomatic or asymptomatic increase in peak TRV > 3.4 m/s.</i> | I | C |
| <i>Dasatinib dose reduction and close monitoring of peak TRV with echocardiography should be considered in patients who develop new asymptomatic peak TRV ranging from 2.9 to 3.4 m/s.</i> | IIa | C |
| <i>In patients with confirmed dasatinib-induced PAH or new asymptomatic peak TRV > 3.4 m/s, an alternative BCR-ABL inhibitor is recommended after peak TRV recovery to < 2.8 m/s.</i> | I | C |

▪ **Pericardial diseases:**

Pericarditis and pericardial effusion can be related to a wide range of cancer treatments including chest radiation, cytotoxic therapies (anthracyclines, bleomycin, cyclophosphamide, cytarabine), targeted therapies (all-trans retinoic acid, arsenic trioxide, dasatinib), and immune-based therapies (interleukin-2, interferon- α ICI).

Table 33-17: ESC Recommendations for the management of pericardial diseases in patients receiving anticancer treatment:

| Recommendations | Class | Level |
|--|--------------|--------------|
| General: | | |
| <i>Diagnosis and management of acute pericarditis in patients with cancer based on the ESC Guidelines for the diagnosis and management of pericardial diseases is recommended and a multidisciplinary discussion is needed before interrupting cancer therapy.</i> | I | C |
| <i>A surgical pericardial window should be considered if the percutaneous approach is not feasible or in cases of recurrent malignant pericardial effusions.</i> | IIa | C |
| <i>Intrapericardial instillation of cytostatic or sclerosing agents may be considered for prevention of recurrence.</i> | IIb | C |
| Diagnosis and management of ICI-associated pericarditis | | |

| | | |
|--|----------|----------|
| <i>Multimodality CV imaging (echocardiography, CMR + CT), ECG and measurement of cardiac biomarkers are recommended to confirm the diagnosis, assess the hemodynamic consequences of pericardial disease, and rule out associated myocarditis.</i> | I | C |
| <i>Prednisolone and colchicine are recommended for patients with ICI-associated pericarditis.</i> | I | C |
| <i>Interruption of ICI treatment in patients with confirmed ICI-associated pericarditis with moderate-to-severe pericardial effusion is recommended.</i> | I | C |
| <i>A multidisciplinary discussion is recommended before restarting ICI treatment.</i> | I | C |

CV risk assessment at the end of cancer therapy:

▪ **Which cancer survivors require CV surveillance in the first year after cancer treatment?**

The end-of-treatment risk assessment ideally identifies those high-risk CS, who require long-term CV surveillance, Risk factors for future CV disease at the end-of-cancer therapy CV risk assessment:

1. High- and very-high baseline CV toxicity risk based on HFA-ICOS assessment.
2. Specific anticancer treatment proven to have a high risk of long-term CV complications:
 - Doxorubicinb $\geq 250 \text{ mg/m}^2$
 - RT $> 15 \text{ Gy MHD}^{(1)}$.
 - Both doxorubicinb $\geq 100 \text{ mg/m}^2$ and RT 5-15 Gy MHD.

(1) RT risk categorization based on MHD is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors), the treatment team may judge the patient to belong to a higher risk category. In addition, a patient may be judged to belong to a lower risk category if only a small part of the heart is exposed to a relatively high prescribed dose (i.e. RT to left breast or left chest wall only).

- High-risk HSCT patients ⁽¹⁾.
- 3. Moderate or severe CTR-CVT during cancer treatment (especially CTRCD), ICI-related myocarditis, cardiac arrhythmias, or severe vascular toxicities (ACS, stroke, PVD).
- 4. New CV symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment.
- **Management of CTRCD at the end-of-therapy assessment:**
 - During this end-of-treatment assessment, a review of cardioprotective medications initiated during cancer therapy to treat CTRCD is recommended. For example, a trial of weaning off CV medication should be considered after MDT discussion after asymptomatic mild or moderate CTRCD secondary to trastuzumab, particularly in younger otherwise healthy HER2+ BC survivors with no exposure to anthracycline chemotherapy.
 - Continuing long-term CV medication is generally recommended in patients with moderate and severe symptomatic or severe asymptomatic CTRCD due to the high rate of recurrent HF. Long-term treatment is also recommended in CS with mild or moderate CTRCD who fail to recover normal LV function at their end-of-therapy assessment.
- **Cardiopulmonary exercise testing and fitness during the end-of-therapy assessment:**

Cardiorespiratory fitness impairment is a strong predictor of patient outcome following cancer treatment and an intervention target in CS. CPET may be considered for CS with exertional limitation, who may have substantial benefit from cardiac rehabilitation. Eligible patients include those treated with higher doses of anthracycline chemotherapy and/or RT to a volume including the heart, high CV toxicity risk at baseline, patients who developed CTRCD during cancer therapy, and those identified with new abnormalities in LV function at their end-of-therapy assessment.

(1) High-risk HSCT patients: *allogenic HSCT; pre-existing CVD or multiple uncontrolled CVRF; cancer treatment history (mediastinal or mantle field radiation, alkylating agents, > 250 mg/m² doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.*

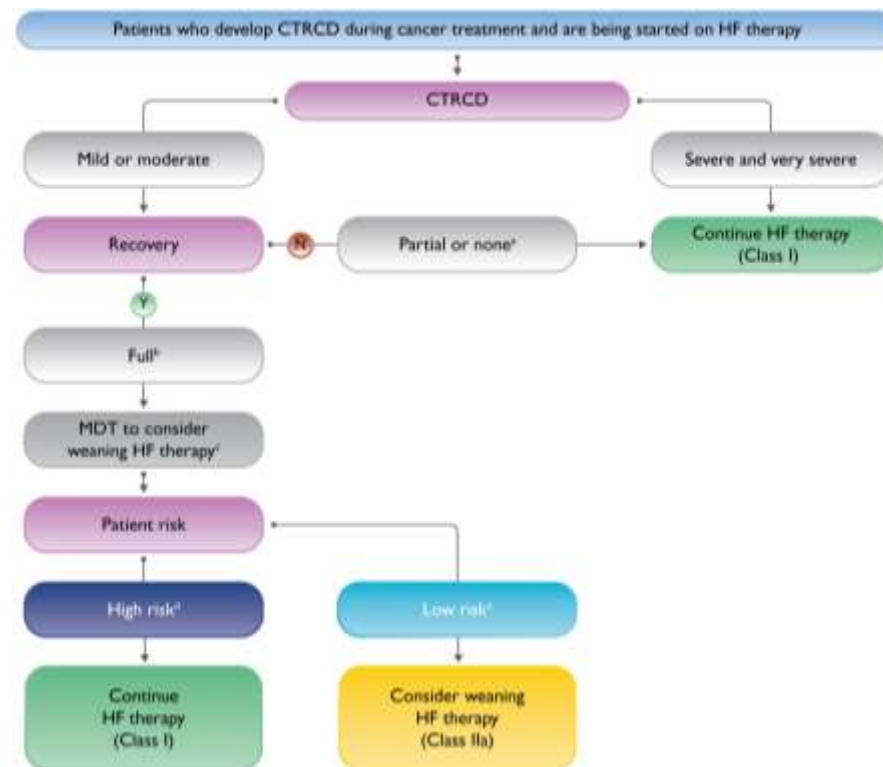


Figure 33-12: Management of cancer therapy-related cardiac dysfunction after cancer therapy. A) Partial or no recovery: patients who do not meet all of the criteria for full recovery. **B)** Full recovery: no signs or symptoms of HF + LVEF . 50% + GLS within normal range or similar to baseline measurements + cardiac serum biomarkers within the normal range or similar to baseline measurements. **C)** The CTRCD trajectory of each patient is unique and dynamic and withdrawal of HF therapy requires a MDT to consider several key points that help to stratify patients into low- or high-risk categories. Key points to consider during a MDT discussion are: HFA-ICOS baseline CV toxicity risk assessment, pre-existing indications for CV medication, class of cancer treatment causing CTRCD (generally reversible vs. generally irreversible), magnitude and duration of CTRCD before recovery, intensity of HF therapy needed to recover LV function, family history of cardiomyopathy or known cardiomyopathy gene carrier. **E)** Low-risk patient characteristics: low to moderate baseline CV toxicity risk (HFA-ICOS risk assessment), no pre-existing indications for CV medication, cancer treatment generally associated with reversible myocardial damage, asymptomatic mild CTRCD, early cardiac function recovery (3–6 months) under HF therapy, no family history of cardiomyopathy. **Source:** 2022 ESC Guidelines on cardio-oncology

| Table 33-18: ESC Recommendations for end-of-cancer therapy cardiovascular risk assessment: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Educating and supporting patients with cancer to make appropriate healthy lifestyle choices is recommended.</i> | I | C |
| <i>Education is recommended for patients with cancer regarding recognition for early signs and symptoms of CVD.</i> | I | C |
| <i>CVRF assessment is recommended during the first year after cancer therapy ⁽¹⁾, and thereafter according to the ESC Guidelines on CVD prevention in clinical practice.</i> | I | B |
| <i>In asymptomatic high-risk patients, echocardiography and cardiac serum biomarkers are recommended at 3 and 12 months after completion of cancer therapy.</i> | I | B |
| <i>In asymptomatic moderate-risk patients, echocardiography and cardiac serum biomarkers should be considered within 12 months after completion of cancer therapy.</i> | IIa | B |
| <i>In asymptomatic low-risk patients ⁽²⁾, echocardiography and cardiac serum biomarkers may be considered within 12 months after completion of cancer therapy.</i> | IIb | C |
| <i>Cardiology referral ⁽³⁾ is recommended in patients with cancer with new cardiac symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment.</i> | I | C |
| <i>In selected patients with exercise intolerance persisting at 12 months after cancer treatment and with normal resting echocardiogram and cardiac biomarkers, exercise stress echocardiography and/or CPET may be considered.</i> | IIb | C |

(1) Including regulation of hypertension, DM, dyslipidemia, smoking cessation, weight loss in case of obesity, and an adequate amount of exercise.

(2) Moderate- or low-risk patients: according to CV toxicity baseline risk stratification.

(3) Cardio-oncology referral is recommended when available; alternatively, the patient should be referred to a cardiologist with expertise in managing CVD in patients with cancer.

| | | |
|--|------------|----------|
| <i>Targeted cardiac rehabilitation should be considered in CS with high CV risk.</i> | IIa | B |
| <i>Long-term continuation of cardiac medication is recommended in patients who develop severe CTRCD during cancer therapy.</i> | I | C |
| <i>CV follow-up and treatment optimization is recommended in patients who developed TKI-mediated hypertension during cancer therapy.</i> | I | C |
| <i>CV follow-up and treatment optimization is recommended in patients who developed vascular toxicities during cancer therapy.</i> | I | C |
| <i>ECG follow-up is recommended in patients who developed QT lengthening or LQTS during cancer therapy.</i> | I | C |

Long-term follow-up and chronic CV complications in cancer survivors:

▪ **Cancer survivors:**

- In paediatric CS, follow-up according to the International Late Effects of Childhood Cancer Guideline Harmonization Group is recommended. This includes risk stratification based upon the total cumulative dose of anthracycline chemotherapy and MHD delivered.
- In adults CS, Long-term follow-up surveillance, based on CV toxicity risks, includes patient education and CVRF optimization. An annual clinical CV risk assessment is recommended for all adult CS to optimize CVRF control, promote a healthy lifestyle, and symptom review.

Table 33-19: Risk categories for asymptomatic adult cancer survivors:

| Risk category ⁽¹⁾ | Patient characteristics |
|-------------------------------------|--------------------------------|
|-------------------------------------|--------------------------------|

(1) RT risk categorization based on MHD is recommended over categorization based on prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors), the treatment team may judge the patient to belong

| | |
|--|---|
| Very high risk | <ul style="list-style-type: none"> ○ Very high baseline CV toxicity risk pre-treatment ○ Doxorubicinb $\geq 400 \text{ mg/m}^2$ ○ RT $> 25 \text{ Gy MHD}$ ○ RT $> 15\text{--}25 \text{ Gy MHD}$ + doxorubicinb $\geq 100 \text{ mg/m}^2$ |
| Early high risk (> 5 years after therapy) | <ul style="list-style-type: none"> ○ High baseline CV toxicity risk ○ Symptomatic or asymptomatic moderate-to-severe CTRCD during treatment ○ Doxorubicinb $250\text{--}399 \text{ mg/m}^2$ ○ High-risk HSCT ⁽¹⁾ |
| Late high risk | <ul style="list-style-type: none"> ○ RT $> 15\text{--}25 \text{ Gy MHD}$ ○ RT $5\text{--}15 \text{ Gy MHD}$ + doxorubicinb $\leq 100 \text{ mg/m}^2$ ○ Poorly controlled CVRF |
| Moderate risk | <ul style="list-style-type: none"> ○ Moderate baseline CV toxicity risk ○ Doxorubicinb $100\text{--}249 \text{ mg/m}^2$ ○ RT $5\text{--}15 \text{ Gy MHD}$ ○ RT $< 5 \text{ Gy MHD}$ + doxorubicinb $\geq 100 \text{ mg/m}^2$ |
| Low risk | <ul style="list-style-type: none"> ○ Low baseline CV toxicity risk and normal end-of-therapy cardiac assessment ○ Mild CTRCD during therapy but recovered by the end of cancer therapy. ○ RT $> 5 \text{ Gy MHD}$. ○ Doxorubicinb $< 100 \text{ mg/m}^2$ |

to a higher risk category. In addition, a patient may be judged to belong to a lower risk category in case only a small part of the heart is exposed to a relatively high prescribed dose.

(1) High-risk HSCT patients: allogeneic HSCT; pre-existing CVD or multiple uncontrolled CVRF; cancer treatment history (mediastinal or mantle field radiation, alkylating agents, $> 250 \text{ mg/m}^2$ doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.

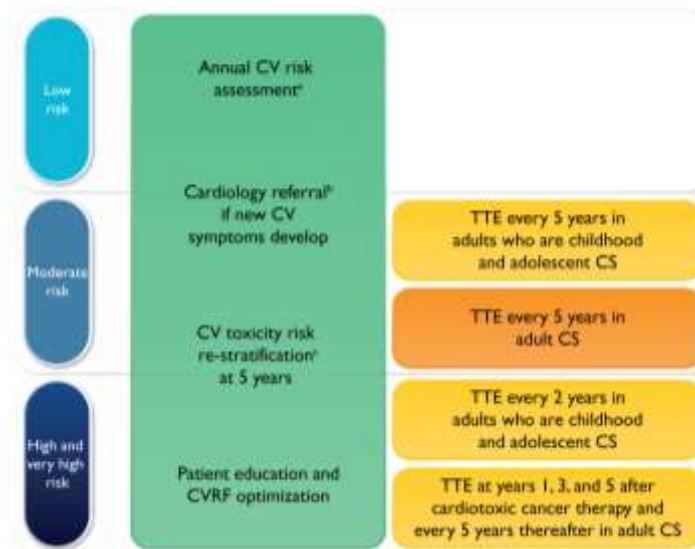


Figure 33-13: Long-term follow-up in cancer survivors. A) Clinical review, BP, lipid profile, HbA1c, ECG, NP. In selected patients, non-invasive screening for CAD and carotid or renal diseases every 5–10 years, starting at 5 years after radiation may be considered. B) Cardio-oncology referral is recommended when available; alternatively, the patient should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer. C) Re-stratification includes evaluation of new or pre-existing CVRF and CVD (including CTR-CVT). **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-20: ESC Recommendations for CV surveillance in asymptomatic adult cancer survivors:

| Recommendations | Class | Level |
|--|-------|-------|
| Asymptomatic adults who are childhood and adolescent cancer survivors | | |
| <i>Education of adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart and their healthcare providers regarding their increased CV risk is recommended.</i> | I | B |

| | | |
|---|------------|----------|
| <i>Annual screening for modifiable CVRF (Obesity, sedentary lifestyle, cigarette smoking, alcohol intake, unhealthy diet, dyslipidemia, hypertension, DM.) is recommended in adults who are childhood and adolescent CS treated with anthracyclines, mitoxantrone, and/or RT to a volume including the heart.</i> | I | C |
| <i>CV assessment (BP, lipids, fasting glucose, HbA1c, ECG, and TTE) is recommended in female childhood and adolescent CS prior to pregnancy or in the first trimester.</i> | I | C |
| <i>Echocardiography surveillance should be considered every 2 years in adults who are high-risk childhood and adolescent CS.</i> | IIa | B |
| <i>Echocardiography surveillance should be considered every 5 years in adults who are moderate-risk childhood and adolescent CS.</i> | IIa | B |
| Asymptomatic adult cancer survivors: | | |
| <i>Annual CV risk assessment, including ECG and NP, and CVRF management is recommended in CS who were treated with a potentially cardiotoxic cancer drug or RT.</i> | I | B |
| <i>CV toxicity risk restratification is recommended 5 years after therapy to organize long-term follow-up.</i> | I | C |
| <i>Echocardiography at years 1, 3, and 5 after completion of cardiotoxic cancer therapy and every 5 years thereafter should be considered in asymptomatic very high- and early high-risk adult CS.</i> | IIa | C |
| <i>Echocardiography should be considered in asymptomatic late high-risk adult CS starting at 5 years after radiation to a volume including the heart and then every 5 years.</i> | IIa | C |
| <i>Echocardiography may be considered every 5 years in asymptomatic moderate-risk adult CS.</i> | IIb | C |
| <i>Non-invasive screening for CAD ⁽¹⁾ should be considered every 5–10 years in asymptomatic patients who received > 15 Gy MHD, starting at 5 years after radiation.</i> | IIa | C |
| <i>Carotid ultrasound imaging should be considered every 5 years in asymptomatic patients with a history of head/neck RT, starting at 5 years after radiation and every 5–10 years thereafter.</i> | IIa | C |

(1) Stress echocardiography, cardiac CT, stress CMR, single-photon emission CT stress test, according to local protocol.

Renal artery ultrasound should be considered in patients with a history of abdominal and pelvic radiation who present with worsening renal function and/or systemic hypertension.

IIa

C

▪ **Myocardial dysfunction and heart failure:**

HF treatment in CS should follow the current ESC Guidelines for the diagnosis and treatment of acute and chronic HF. In CS with mild asymptomatic CTRCD detected on CV assessment (LVEF > 50% but new fall in GLS and/or cardiac serum biomarker increase), treatment with ACE-I/ARB and/or beta-blockers may be considered.

Table 33-21: ESC Recommendations for adult cancer survivors who develop cancer therapy-related cardiac dysfunction late after cardiotoxic cancer therapy:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|--------------|--------------|
| <i>ACE-I/ARB and/or beta-blockers are recommended in adult CS with moderate asymptomatic CTRCD.</i> | I | C |
| <i>ACE-I/ARB and/or beta-blockers may be considered in adult CS with mild asymptomatic CTRCD.</i> | IIb | C |

▪ **Coronary artery disease:**

Any vascular location within the RT treatment volume is at increased risk for both accelerated atherosclerosis and RT-related vasculopathy. The latency between RT and the appearance of CAD varies from a few years to several decades, depending upon the presence or absence of pre-existing atherosclerosis and the age of the patient at the time of RT.

Table 33-22: ESC Recommendations for adult cancer survivors with coronary artery disease:

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|--|--------------|--------------|
| Asymptomatic radiation-induced CAD detected during surveillance: | | |
| <i>Non-invasive stress testing is recommended in asymptomatic CS with new moderate or severe radiation-induced CAD detected on CCTA to guide ischemia-directed management.</i> | I | C |

| | | |
|---|------------|----------|
| <i>A MDT discussion is recommended for clinical decision-making in patients with radiation-induced CAD and inducible ischemia or severe left main CAD.</i> | I | C |
| Symptomatic CAD | | |
| <i>Pre-operative assessment of LIMA and RIMA viability, venous access, and sternal wound healing is recommended in CS with radiation-induced CAD where CABG is considered.</i> | I | C |
| <i>PCI may be considered in CS with radiation-induced CAD with severe left main or three-vessel disease with a high SYNTAX score (> 22) in whom the procedure is technically feasible.</i> | IIb | C |

▪ **Valvular heart disease:**

VHD can appear in CS at any point in time but typically occurs 10 or more years after cancer treatment. Chest RT is the main risk factor in CS, in particular at higher dose ranges, which can cause either stenosis or regurgitation, or both.

| Table 33-23: ESC Recommendations for adult cancer survivors with valvular heart disease: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>A MDT approach is recommended to discuss and define the surgical risk ⁽¹⁾ in CS with severe VHD.</i> | I | C |
| <i>TAVI should be considered for patients with symptomatic severe aortic stenosis caused by radiation at intermediate surgical risk.</i> | IIa | B |

▪ **Pulmonary hypertension:**

Long-term clinical evaluation may be considered in patients who develop PH during therapy. In patients with new exertional dyspnoea, fatigue, or angina, a TTE is recommended to assess the probability of PH. As TTE alone is not enough to confirm the

(1) Surgical risks include: vascular access, sternal and skin wound healing, concomitant cardiac disease, radiation-induced lung and thoracic vessels disease, aortic calcification, STS PROM/EuroSCORE II.

diagnosis of PH, CS diagnosed with high PH probability require a right-heart catheterization to confirm the diagnosis. PH should be treated according to general guidelines with referral to a specialist PH service.

▪ **Pregnancy in cancer survivors:**

| Table 33-24: ESC Recommendations for cardiovascular monitoring in cancer survivors during pregnancy : | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>In high-risk female CS, pre-pregnancy counselling and management during pregnancy and around delivery by a multidisciplinary pregnancy heart team is recommended.</i> | I | C |
| <i>A baseline CV evaluation including history, physical examination, ECG, NP, and echocardiography is recommended in female CS with a history of CTRCD who are considering pregnancy.</i> | I | C |
| <i>A baseline CV evaluation including history, physical examination, ECG, and echocardiography should be considered in all female CS who received potentially cardiotoxic cancer therapy and are considering pregnancy.</i> | Ila | C |
| <i>A CV evaluation including echocardiography is recommended at 12 weeks of pregnancy in female CS who are either high-risk or who received potentially cardiotoxic cancer therapy and did not have a baseline CV assessment.</i> | I | C |
| <i>A second CV evaluation including echocardiography should be considered at 20 weeks of pregnancy in high-risk female CSc who received potentially cardiotoxic cancer therapy.</i> | Ila | C |

Special populations:

▪ **Pregnant patients with cancer:**

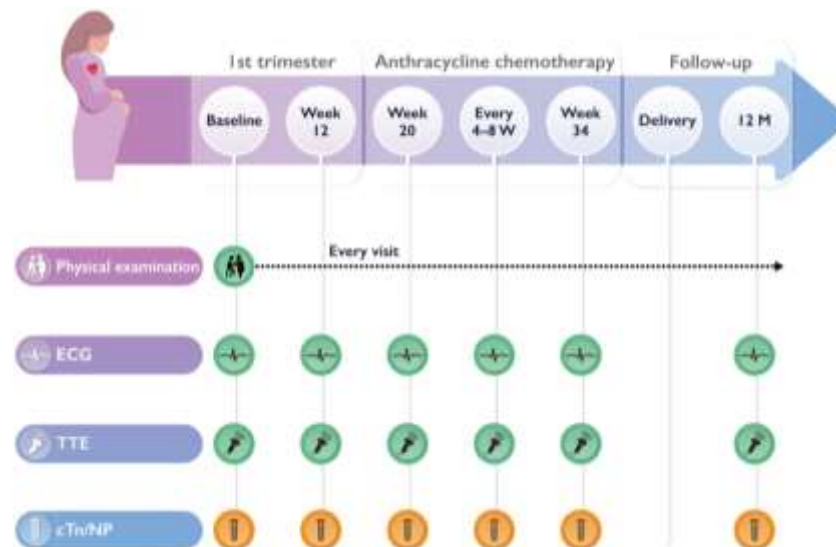
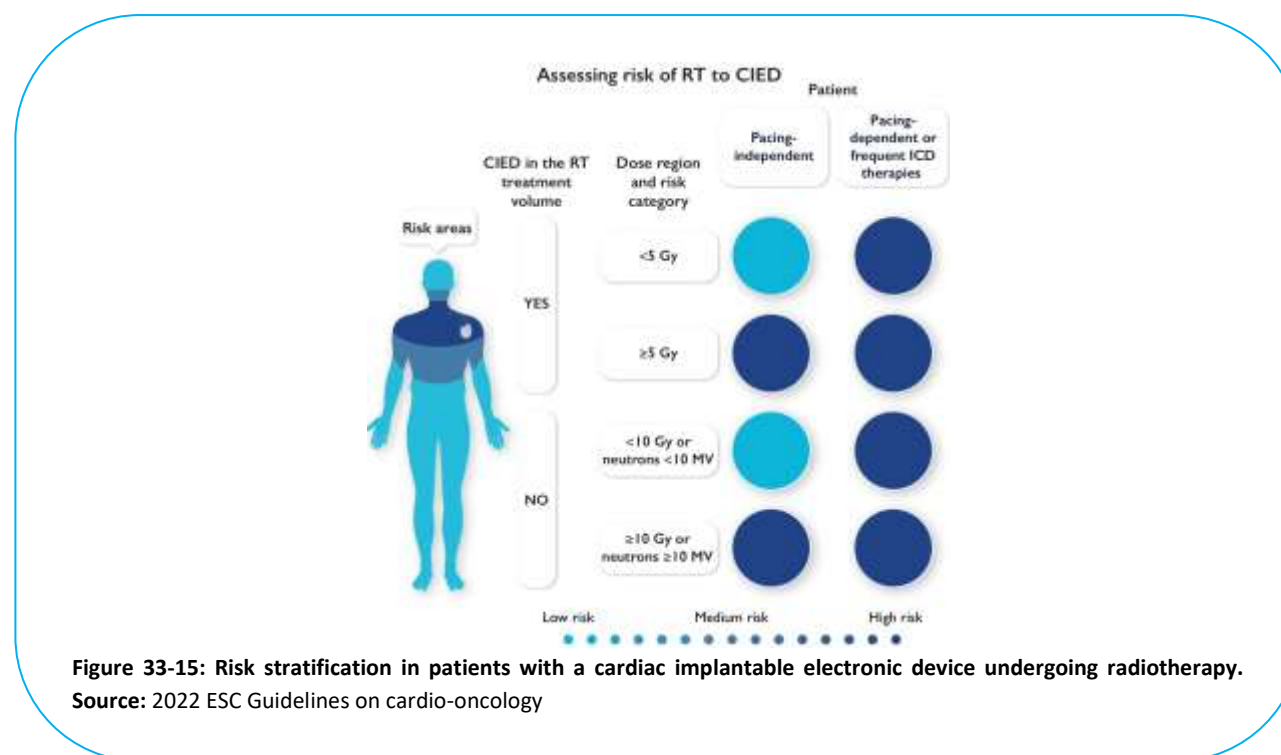


Figure 33-14: Cardiac monitoring protocol for pregnant women receiving anthracycline-based chemotherapy. Source: 2022 ESC Guidelines on cardio-oncology

| Table 33-25: ESC Recommendations for cardiovascular assessment and monitoring of pregnant women with cancer: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Management by an expert MDT (the pregnancy heart team) in an expert centre is recommended for pregnant women with cancer who require cardiotoxic cancer therapy.</i> | I | C |
| <i>Cardiac assessment prior to cardiotoxic cancer therapy in pregnant women is recommended and consists of clinical history, physical examination, ECG, and echocardiography.</i> | I | C |
| <i>Monthly or bimonthly CV evaluation, including TTE, should be considered during cardiotoxic cancer therapy in pregnant women with cancer.</i> | IIa | C |
| <i>cTn may be considered at baseline and during anthracycline chemotherapy in pregnant women with cancer.</i> | IIb | C |

- **Cardiac implantable electronic Devices (CIEDs):**

RT can cause malfunction of CIEDs. The risk of RT-induced CIED malfunction generally increases with the radiation dose, although the strongest predictor of malfunction is the magnitude of exposure to neutron emission from high-energy photon RT, conventionally defined as a beam energy > 10 megavolts. RT-induced CIED malfunction can manifest in: **(1)** transient interference, with inappropriate triggering during the irradiation only; **(2)** a reset, reverting to backup settings, recoverable with device reprogramming; and, rarely **(3)** permanent damage to the device due to direct CIED irradiation. Patients with a CIED should be reviewed by their cardiologist/electrophysiologist to assess the risk of CIED malfunction and patients should be informed of the potential risks of RT.



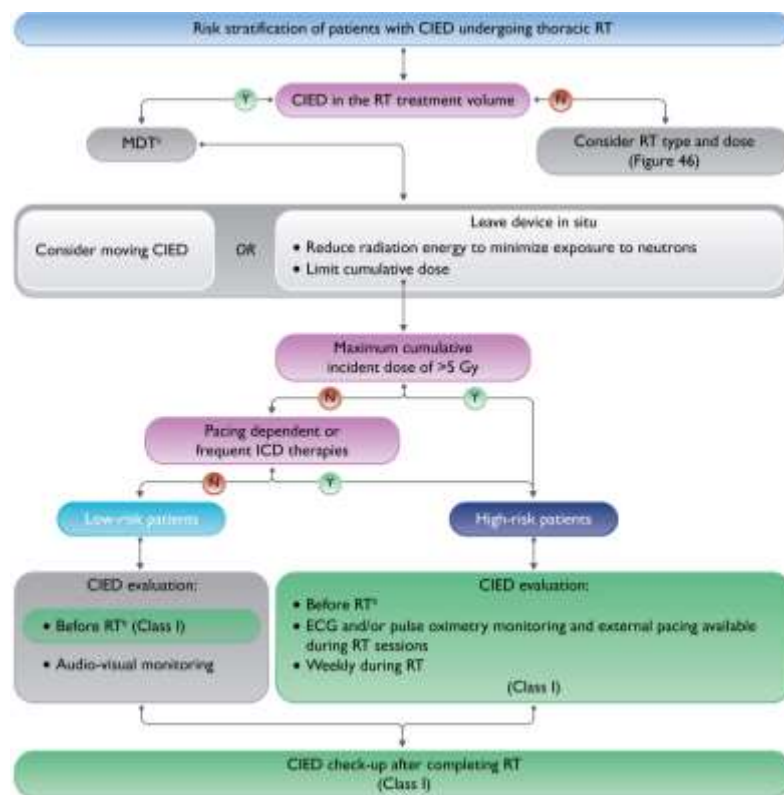


Figure 33-16: Management of patients with a cardiac implantable electronic device located in the radiotherapy treatment beam. A) Multidisciplinary discussion must consider: (1) whether the CIED is interfering with the RT dose delivered to the tumour; (2) whether the RT is interfering with CIED function (aim to not exceed 2 Gy to permanent pacemaker and 1 Gy to ICD); (3) risks of moving the CIED: infection (especially in immunocompromised patients), procedural complications (e.g. bleeding with thrombocytopaenia); for younger patients with good prognosis, consider long-term effects of losing an access site (lead extraction/RT-induced thrombosis). **B)** If last CIED check > 3 months earlier. **Source:** 2022 ESC Guidelines on cardio-oncology

Table 33-26: ESC Recommendations for risk stratification and monitoring for patients with cardiac implantable electronic devices undergoing radiotherapy:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Risk stratification including planned radiation type and energy, dose to CIED, the patient's device type, and pacing dependence is recommended prior to starting treatment.</i> | I | C |
| <i>In patients undergoing RT, a CIED check is recommended in all patients before and after completing RT, and during RT according to individual risk.</i> | I | C |
| <i>In patients with a CIED undergoing RT at high risk of arrhythmia and/or device dysfunction, ECG monitoring and/or pulse oximetry are recommended during every RT session.</i> | I | C |

Radiation Heart Disease

- Radiation heart disease leads to calcification of the cardiac valves and fibrous skeleton, with cardiac abnormalities becoming evident over 5–10 years, sometimes decades, after radiation.
- The pericardium is the cardiac structure that is most sensitive to radiation and is the most common site of clinical involvement (constrictive pericarditis). The aortic valve is the valve most commonly affected, the combination of AS and AI being the most common radiation-induced valvular disease. MR is also common (second in frequency), followed by TR.
- The early process consists of fibrosis of the aortic and mitral annuli with subsequent valvular retraction and regurgitation. This is followed by progressive thickening and calcification of the valves but also the cardiac skeleton and mitroaortic curtain. As opposed to rheumatic disease, the mitral base is involved but the mitral leaflets' tips and commissures are spared.
- In addition, radiation leads to: (1) ostial or diffuse CAD, mainly involving the left main, ostial RCA, or LAD (anterior); (2) myocardial fibrosis with restrictive cardiomyopathy and sometimes LV systolic dysfunction (usually mild); and (3) heavily calcified porcelain aorta.

- All this complicates the valvular surgery and limits its efficacy. The severe calcifications limit the size of the aortic prosthesis that can be implanted. In addition, interstitial lung disease, recurrent pleural effusions, and impaired skin and sternal healing complicate the operation.
- While senile mitral annular calcifications are usually posterior, anterior mitral annular calcifications on the long-axis view always suggest radiation heart disease. This corresponds to calcification of the mitroaortic intervalvular fibrosa.

Cardiac tumors

Classification:

Cardiac tumors are classified as either primary or secondary (metastases).

Cardiac metastases are much more common than primary cardiac tumors.

Over 90% of primary cardiac tumors are benign (myxomas are predominant in adults, rhabdomyomas in children). Malignant primary tumors most commonly consist of sarcomas (approximately 65%) or lymphomas (approximately 25%).

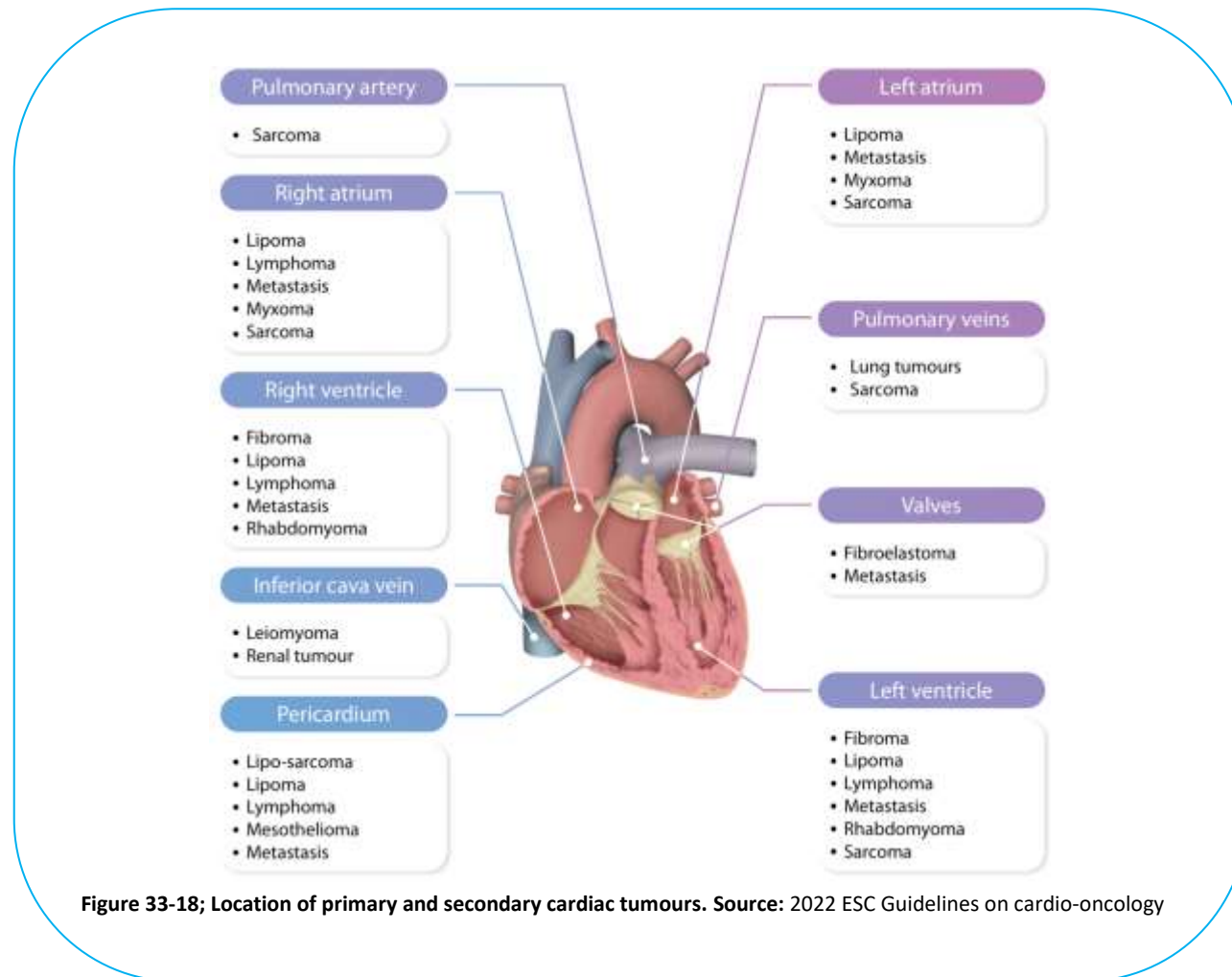
Diagnosis:

Presenting symptoms are paraneoplastic (fever, weakness, fatigue), thromboembolic, hemodynamic (due to compression or obstruction from the tumor) or arrhythmic.

The diagnostic pathway should be based on knowledge about tumor type epidemiology, imaging features, and usually the requirement for a histopathological diagnosis.

Differential diagnosis:

Differential diagnosis should exclude cardiac thrombi or the presence of chemotherapy catheters. Imaging must assess the possibilities of cardiac surgery, and may include: **(1)** echocardiography (initial approach using TTE or transoesophageal echocardiography); **(2)** CMR (for cardiac tumor tissue characterization); and **(3)** CT and PET (to distinguish malignant from benign lesions and assess for non-cardiac metastatic disease or primary cancers).



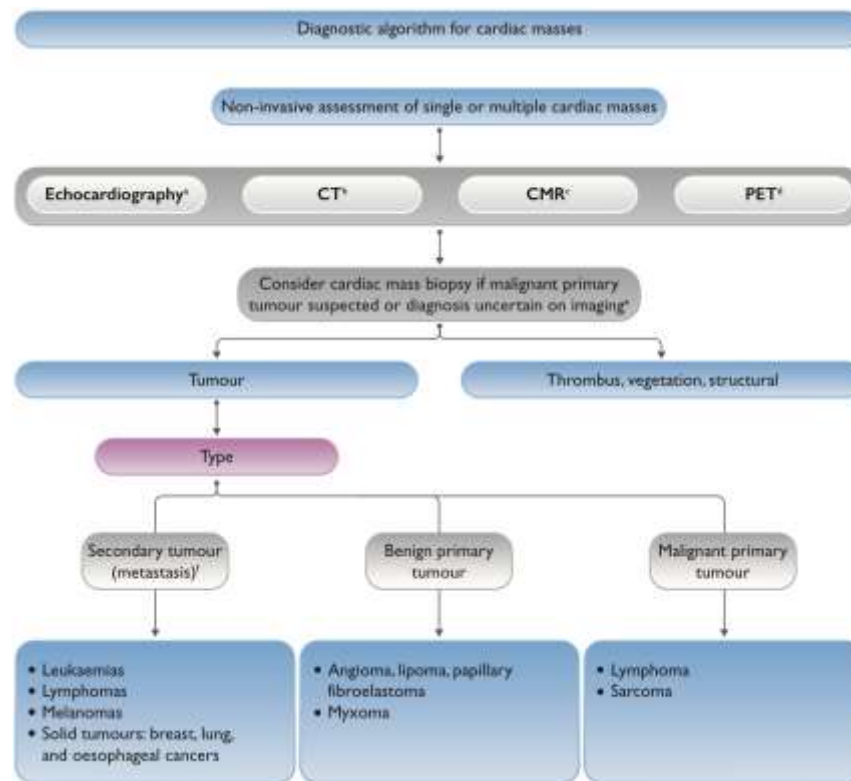


Figure 33-19: Diagnostic algorithm for cardiac masses. **A)** TTE/transoesophageal echocardiography: location, size, and hemodynamic disturbances. Contrast echocardiography to assess vascularization. **B)** Identify primary extra-cardiac malignancy. Reveal extra-cardiac changes. Staging of malignant lesions. **C)** Tissue characterization (fat infiltration, necrosis, hemorrhage, calcification, and vascularization). Exclude thrombus. **D)** Distinguish malignant vs. benign lesions. Staging of malignant lesions. **E)** Mass biopsy of suspected primary malignant cardiac tumors and/or biopsy of extracardiac masses if detected and safer to biopsy. **F)** 20–30 times more likely than primary tumours.

Source: 2022 ESC Guidelines on cardio-oncology

Management:

Myxomas are primarily treated with surgery with a good prognosis.

Malignant tumors are associated with a poor prognosis and evidence of the best treatment is lacking. Complete surgical resection is often impossible and adjuvant RT, systemic chemotherapy, and/or debulking palliative surgery are needed.

Cardiac aggressive B-cell lymphomas require histopathological diagnosis (often obtained via analysis of pericardial effusion, EMB, or direct surgical biopsy) and are treated with chemotherapy, followed by RT.

Table 33-27: Management strategies and surgery indications for symptomatic and asymptomatic patients with benign and malignant cardiac tumors:

| Classification | Management strategies | Surgery indications |
|-------------------------|--|--|
| Benign tumors | | |
| Asymptomatic | MDT discussion is required considering: tumor type, location, size, growth rate, and likelihood of embolism. Anticoagulation should be considered for left-sided tumors or right-sided tumors associated with an intracardiac shunt, according to the individual's embolic and bleeding risk | If left-sided and endocardial: even if small and incidental, a MDT is needed to consider the indication for surgical removal due to the embolic risk |
| Symptomatic | Non-surgical management for: <ul style="list-style-type: none">- Rhabdomyomas (possible spontaneous regression)- Intramural hemangioma (possible response to corticosteroids)- Unresectable cases: if antiarrhythmic therapy is suffice | <ul style="list-style-type: none">• Surgical resection is indicated in all other cases.• For large, benign, unresectable, symptomatic cardiac tumors (obstruction, severe HF, or malignant arrhythmias), heart transplantation may be indicated in some cases |
| Malignant tumors | | |

| | | |
|---------------------|--|---|
| Asymptomatic | Histopathological diagnosis is required | If primary cardiac sarcoma, a complete surgical resection may increase survival |
| Symptomatic | <ul style="list-style-type: none"> - Chemotherapy and/or RT are the only options for secondary cardiac tumors. - If primary cardiac lymphoma: chemotherapy | Secondary cardiac tumors may also be treated with palliative cardiac surgery |

Carcinoid valvular heart disease

- Carcinoid tumors are rare neuroendocrine malignancies originating from the enterochromaffin cells.
- Carcinoid syndrome is a rare cause of acquired VHD including mainly right-sided valvular lesions, but also left-sided involvement ⁽¹⁾, pericardial effusion, and myocardial metastases.
- Coronary artery vasospasm and paroxysmal atrial or ventricular tachycardias may rarely occur due to sympathetic stimulation.
- Approximately 20% of patients with neuroendocrine malignancies develop carcinoid syndrome (7.6–32.4%), which is associated with shorter survival (4.7 years compared with 7.1 years in patients without carcinoid syndrome) and poor quality of life.
- **Screening:**
 - NP should be considered for screening and surveillance of patients at risk of carcinoid cardiac involvement and TTE is recommended in patients with NT-proBNP > 260 pg/mL or clinical signs or symptoms.
 - In asymptomatic patients with NT-proBNP < 260 pg/ mL, repeat clinical and NP assessment should be considered every 6 months.
- **Treatment:** Survival has improved in carcinoid tumors, with the use of somatostatin analogues and surgical techniques in liver metastasis. However, right HF still represents a major cause of death.

1) *In the presence of a patent foramen ovale, interatrial shunt, primary bronchial neuroendocrine tumor, or extensive liver metastases, humoral substances directly enter the systemic circulation, causing left-sided valvular involvement in up to one-third of cases.*

- **Surgery:** Many patients with severe tricuspid regurgitation due to carcinoid syndrome require both tricuspid and pulmonary valve surgery.
- Administration of i.v. somatostatin analogues (e.g. octreotide) is recommended to avoid a perioperative carcinoid crisis. The infusion should be started on the morning of the procedure (up to 12 h pre-operatively), continued throughout the procedure (surgery, pre-operative coronary angiography, pacemaker implantation), and post-operatively for at least 48 h following valve surgery or until stable if a carcinoid crisis is triggered post-operatively.
- The optimal choice of valve prosthesis is still a matter of debate due to the balance of risk of both accelerated bioprosthetic valve de- generation vs. bleeding risks in patients with extensive liver metastases requiring therapeutic anticoagulation for mechanical valves.
- Complications include: (i) AV block, requiring pacemaker implantation in 25% of patients. (ii) RV dysfunction: reduced RV function does not improve despite tricuspid valve replacement and HF persists. (iii) Thrombus formation on the tricuspid bioprosthesis can occur, especially during the first 3 months post-operatively, and oral anticoagulation with VKA may be considered. (iv) Persistent serotonin elevation can cause recurrent bioprosthesis valve fibrosis. Valve-in-valve trans-catheter intervention has been reported in bioprosthetic valve failure in metastatic carcinoid heart disease.
- In patients with left-sided carcinoid valvular involvement, closure of interatrial shunts should be considered, although only sparse data exist for this approach.

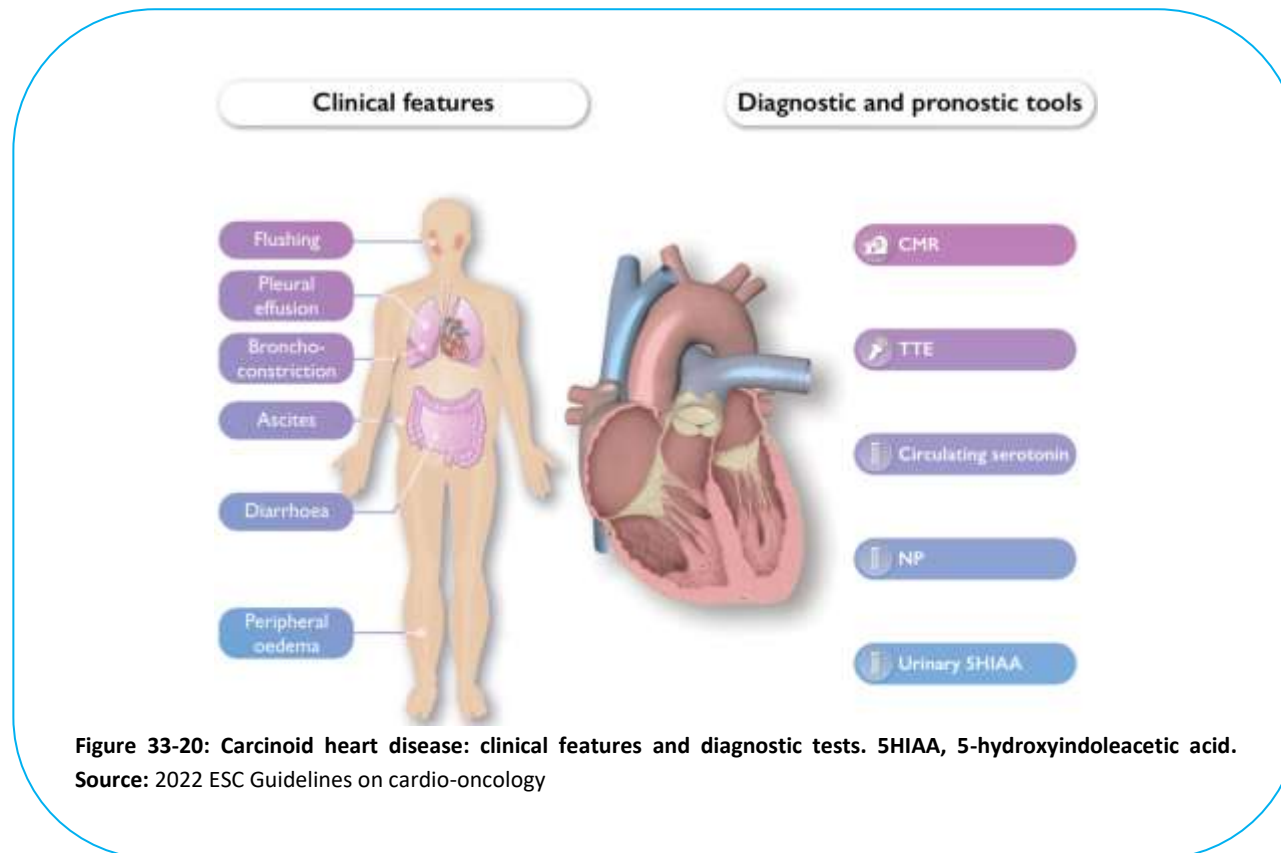


Figure 33-20: Carcinoid heart disease: clinical features and diagnostic tests. 5HIAA, 5-hydroxyindoleacetic acid.
Source: 2022 ESC Guidelines on cardio-oncology



| Table 33-28: ESC Recommendations for carcinoid valvular heart diseases: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Echocardiography (Including saline contrast infusion at baseline to rule out PFO) is recommended for the detection of carcinoid cardiac involvement in all patients with carcinoid syndrome and elevated NP levels and/or clinical signs of carcinoid heart disease, and for surveillance every 3 or 6 months depending on the severity of cardiac involvement and clinical status. | I | B |
| NP should be considered for screening and surveillance of carcinoid heart disease every 6 months. | Ila | B |



| | | |
|---|------------|----------|
| <i>A MDT discussion for optimal medial management to prevent carcinoid crisis is recommended before any invasive or surgical cardiac procedure.</i> | I | C |
| <i>Valve replacement surgery is recommended in symptomatic patients with severe carcinoid tricuspid or pulmonary VHD and an expected survival ≥ 12 months (With controlled serotonin concentrations).</i> | I | C |
| <i>Valve replacement surgery should be considered in patients with asymptomatic severe carcinoid tricuspid or pulmonary VHD, progressive RV dysfunction/dilatation, and an expected survival ≥ 12 months.</i> | Ila | C |
| <i>Valve replacement or repair surgery is recommended in symptomatic patients with severe carcinoid mitral or aortic VHD and an expected survival ≥ 12 months.</i> | I | C |



References and suggested readings:




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- Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.
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Table 33-29: Cardiac Masses characteristics:

| | Features | Illustration |
|------------------------------|---|---|
| Thrombus | <ul style="list-style-type: none"> ○ Subacute (methemoglobin)- high T2. low T2. ○ Chronic- Iso/low T1 & T2. ○ Slightly hypoattenuating (35-60 HU) ○ Look for signs of underlying infarction- fatty metaplasia ○ DD: Pseudothrombus/mixing (Also seen in LAA. > 80 HU. Disappears on delayed phase). |  |
| Benign primary tumor: | | |
| Myxoma | <ul style="list-style-type: none"> ○ Myxoma is the most common primary cardiac tumor in adults. ○ Typically have a <u>narrow stalk</u> connected to the <u>fossa ovalis</u>. Approximately 75% of cardiac myxomas occur in the <u>left atrium (75%)</u>, the right atrium (15-20%), less often in the RV or LV. ○ Cardiac myxomas may occasionally be found on the posterior wall of the left atrium. However, this location within the left atrium should raise the suspicion for a malignant cardiac tumor. ○ Symptoms result from intracardiac obstruction, systemic embolization, or constitutional symptoms (due to the tumor's synthesis and secretion of <u>IL-6</u>). <u>Dyspnea is the most common symptom</u>. ○ Myxomas are vascular; blood vessels may be seen on color flow imaging and enhanced mildly with transpulmonary contrast agent. ○ Once the likely diagnosis of cardiac myxoma is made based on echocardiography, resection is recommended because of the risk of embolization or cardiovascular complications. ○ The operative mortality is reported to be < 5%. |  |

| | | |
|----------------------|---|---|
| | <ul style="list-style-type: none"> ○ When atrial myxomas arise in unusual locations and multiple tumors are present, think Carney syndrome | |
| Fibroelastoma | <ul style="list-style-type: none"> ○ <u>Second most common</u> primary cardiac tumor <u>in adults</u>. It accounts for approximately 85% of valve-associated tumors. ○ The tumor are small (<20 mm), round or oval, with well-demarcated borders and a homogeneous texture. ○ Nearly half have small stalks, and those with stalks are mobile. ○ Can occur on any valve as <u>single lesion (90%)</u>, but most commonly involve the <u>aortic valve</u>, followed by the mitral valve (rare valve dysfunction). Much less commonly, it can occur on papillary muscle, chordae tendineae, or in the atria. ○ Most often attach to the arterial side of semilunar valves and the atrial surface of the atrioventricular valves. ○ The distinction between papillary fibroelastomas and vegetations can be difficult by echocardiography. Therefore, the correct diagnosis often depends on the clinical context. ○ Surgical resection is indicated in patients who have had embolic events, complications that are directly related to tumor mobility (i.e., coronary ostial occlusion), and those with highly mobile or large (> 1 cm) tumors. ○ Recurrence after surgical resection is rare, but well described in the literature. |  |
| Rhabdomyoma | <ul style="list-style-type: none"> ○ Rhabdomyomas are myocardial hamartomas or malformations that are composed of myocytes rather than true neoplasms. ○ Found in the <u>ventricular walls</u> or on the <u>atrioventricular valves</u>. Can be diagnosed before birth with fetal echocardiography. ○ The microscopic hallmark is the <u>Spider cell</u> (large cell containing central cytoplasmic mass suspended by myofibrillar processes). |  |

| | | |
|----------------|--|---|
| | <ul style="list-style-type: none"> ○ At least <u>80% of patients</u> with rhabdomyomas have <u>tuberous sclerosis</u> (<u>autosomal-dominant</u>). ○ <u>≥ 50% regress spontaneously after infancy</u>. Therefore, in the absence of symptoms, surgery is not indicated. The most appropriate management strategy is reassurance + follow-up echocardiography in 1 year + family screening for affected siblings. | |
| Fibroma | <ul style="list-style-type: none"> ○ Benign connective tissue tumors derived from fibroblasts that <u>occur predominantly in children</u> (most are < 10 years). ○ Fibromas are the <u>second most common</u> type of primary cardiac tumors occurring <u>in children</u>. ○ Typically <u>large</u> tumors, usually occur within the <u>ventricular myocardium</u>, most commonly in the LV <u>anterior wall</u>. ○ About <u>70% of patients are symptomatic</u>. The most common manifestations are <u>congestive HF and ventricular tachyarrhythmias</u>. ○ <u>Resection is usually recommended in asymptomatic patients</u> (due to the risk of fatal arrhythmias). ○ Sudden death has been reported to occur in approximately 15% of patients, typically in infants |  |
| Lipoma | <ul style="list-style-type: none"> ○ Usually asymptomatic. ○ LV > RA. Subendocardial > subepicardial > intramyocardial ○ Subepicardial tumor can get very large. |  |

| | | |
|--------------------------|--|--|
| Hemangioma | <ul style="list-style-type: none"> ○ Any age usually asymptomatic. ○ May be associated with GI hemangiomas. Any chamber or wall. Usually, intramural. ○ Heterogenous on CT. Iso/hyper on T1, hyper on T2. ○ Enhancement, sometimes with central core. Heterogenous LGE. Isointense to hyperintense on first pass perfusion. ○ DD: Teratoma (Hypointense on FPP. Seen in neonates. Both are mixed solid/cystic on CT. Teratoma usually attach to base of PA or aorta. May compress SVC. |  |
| Malignant tumors: | | |
| Angiosarcoma | <ul style="list-style-type: none"> ○ Occurs in the right heart, particularly <u>the right atrium</u>. They can be either intracavitary or diffuse and infiltrative. ○ The common presentation is <u>right-sided heart failure or cardiac tamponade</u> as well as constitutional symptoms. ○ 3:1 male-to-female ratio (unlike other sarcomas, which have a 1:1 ratio). ○ Very poor prognosis. Usually large or have metastasized at the time of diagnosis. Not amenable to complete resection. |  |
| Leiomyosarcoma | <ul style="list-style-type: none"> ○ Derived from smooth muscle cells and may originate from the smooth muscle cells lining the pulmonary veins. ○ Typically present in their 30s, a decade younger than with other types of sarcomas. ○ Often occurs in the <u>left atrium</u>, may originate from the posterior wall of LA and involve the pulmonary veins (Unlike myxomas). ○ Poor prognosis, with a mean survival after surgery of < 7 months. ○ Radical surgical resection is the treatment of choice. ○ The preferential LA location and the frequently myxoid appearance of leiomyosarcomas makes them difficult to differentiate preoperatively from atrial myxomas |  |

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| Lymphoma | <ul style="list-style-type: none"> - Rare form of <u>non-Hodgkin's</u> lymphoma often restricted to <u>right-sided heart chambers</u> and/or pericardium. - Approximately 50% of patients with primary cardiac lymphoma will have <u>large pericardial effusions</u>. <ul style="list-style-type: none"> ○ Rapidly evolves and has been considered an oncologic emergency requiring rapid tissue diagnosis to institute chemotherapy. |  |
| Pericardial cyst | <ul style="list-style-type: none"> ○ Usually asymptomatic. ○ Anomalous outpouching of parietal pericardium. ○ Right > left cardiophrenic angle. ○ DDx: bronchogenic cyst (around carina). Pericardial fat pad. Lobulated pleural effusion. |  |
| Normal Anatomical variants: | | |
| Lipomatous hypertrophy of interatrial septum | <p>The atrial septum is infiltrated by lipomatous material that results in thickening of the inferior and superior portions. The fossa ovalis is spared and results in a “dumb bell-shaped” appearance on 2D echocardiography. Lipomatous hypertrophy of the atrial septum can mimic atrial masses such as myxomas.</p> <p>It is a benign condition, usually does not commonly cause symptoms, however, there is a reported association with atrial arrhythmias and superior vena cava obstruction (if massive).</p> |  |
| Crista Terminalis | <ul style="list-style-type: none"> ○ The crista terminalis has been misinterpreted as a right atrial tumor or thrombus. The crista terminalis originates at the junction of the right atrium and SVC and runs longitudinally toward the IVC. The crista terminalis separates the trabeculated appendage of the atrium from the smooth tubular portion. | |
| Eustachian Valve | <ul style="list-style-type: none"> ○ Eustachian valve is a remnant of the embryologic valve responsible for directing IVC blood across the atrial septum to the LA. It is a rigid and protuberant structure that arises along | |

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|----------------------------|---|--|
| | the posterior margin of the IVC to the border of the fossa ovalis. Although usually immobile, it may occasionally demonstrate independent motion within the RA. | |
| Chiari Network | <ul style="list-style-type: none"> ○ The Chiari network is a congenital remnant of the right valve of the <i>sinus venosus</i>. It consists of a network of fibers in the RA that originate from a region of the Eustachian valve at the orifice of the IVC with attachments to the upper wall of the RA or atrial septum. Chiari networks are present in 2%–3% of normal hearts. Chiari networks are usually not clinically significant although their role in cryptogenic stroke, in association with a patent foramen ovale or atrial septum aneurysm, is controversial ⁽¹⁾ | |
| Coumadin Ridge | <ul style="list-style-type: none"> ○ A prominent muscle ridge is formed between the LAA and the atrial insertion of the left upper pulmonary vein. This prominence is often misdiagnosed as thrombus and is referred to as the <i>Coumadin ridge</i> or “<i>Q-tip</i>” sign. The lack of mobility and characteristic location help distinguish it from an abnormal structure. | |
| Lambl Excrecences | <ul style="list-style-type: none"> ○ Thin filamentous structures attached to the leaflet margin of the aortic valve of elderly patients. These structures can be differentiated from valvular vegetations by their characteristic “delicate” appearance in the absence of any clinical evidence of endocarditis. | |
| Node of Arantius | <ul style="list-style-type: none"> ○ nodular thickening of the central portion of the leaflet edge and is best visualized from the short-axis view of the valve. | |
| Pericardial Sinuses | <ul style="list-style-type: none"> ○ Pericardial sinuses (or folds) between the atria and great vessels can give rise to echolucent spaces despite only minimal amounts of pericardial fluid. The transverse and oblique sinuses of the pericardium can easily mimic pericardial cysts or abscesses. Pericardial fat seen in these extracardiac structures can also mimic intracardiac thrombus | |

(1) Eustachian valve should be differentiated from a Chiari network, which is a delicate-appearing, highly mobile, membranous structure arising near the orifice of the IVC .

Eustachian valve and Chiari Network can be differentiated from thrombus by their characteristic “insertion” into the atrial wall.

| | | |
|--|---|--|
| Moderator Band and False Tendon | <p>The moderator band of the RV has been misinterpreted as an intracardiac mass. This specialized cardiac trabeculation runs from the RV free wall to the interventricular septum.</p> <ul style="list-style-type: none"> ○ In contrast, a false tendon is an anatomic variant of the LV consisting of fibromuscular string(s) coursing from the interventricular septum to the region about the papillary muscles. They can be mistaken for subaortic membranes and pseudoaneurysm. | |
|--|---|--|

Chapter 34:

Sports cardiology

Regular physical activity (PA) is an important component of therapy for most CVDs and is associated with reduced CV and all-cause mortality. Although proportionately scarce, exercise may paradoxically trigger sudden cardiac arrest (SCA) in individuals with CVD. Sports cardiology is a relatively novel and emerging sub-speciality that aim to: **(i)** evaluate an individual's CV risk factors and assess their suitability for sports participation, **(ii)** minimize the risk of adverse events in highly trained athletes during sports participation, **(iii)** conduct pre-participation CV screening to identify athletes at risk of sudden cardiac death or other CV complications during exercise, and **(iv)** accurately diagnose and manage CV conditions in athletes and active individuals.

Definitions:

- **Physical activity** is defined as any bodily movement produced by the skeletal muscle that raises energy expenditure above the resting metabolic rate of 3.5 mL O₂/min/kg, or 1 metabolic equivalent.
- **Exercise or exercise training**, is defined as physical activity that is structured, repetitive, and purposeful to improve or maintain one or more of the five components of physical fitness:
 1. Morphological component (body mass relative to height, body composition, subcutaneous fat distribution, abdominal visceral fat, bone density, and flexibility).
 2. Muscular component (power or explosive strength, isometric strength, muscular endurance).
 3. Motor component (agility, balance, coordination, speed of movement).
 4. Cardiorespiratory component (endurance or submaximal exercise capacity, maximal aerobic power, heart function, lung function, BP).
 5. Metabolic component (glucose tolerance, insulin sensitivity, lipid and lipoprotein metabolism, substrate oxidation characteristics).

- **Athlete** is 'an individual of young or adult age, either amateur or professional, who is engaged in regular exercise training and participates in official sports competition'.
- As a subcategory of physical activity, **Recreational exercise** is defined as any planned, structured, and repetitive action that is pursued to maintain or improve physical fitness/health. Recreational athletes seek the psychological health benefits of exercise rather than competition.
- In contrast, a **competitive athlete** participates in organized team or individual sporting competitions, places a high premium on achievement, and performs systematic training.

In a proposed classification of athletes based on the minimum volume of exercise: '**Elite**' athletes (i.e. national team, Olympians, and professional athletes) generally exercise ≥ 10 h/week; '**Competitive**' athletes [i.e. high school, college, and older (master) club level athletes] exercise ≥ 6 h/week; and '**Recreational**' athletes exercise ≥ 4 h/week. This distinction is somewhat arbitrary since some recreational athletes, such as long-distance cyclists and runners, engage in exercise at higher volumes than some professional athletes participating in skill sports.

Exercise and CV adaptations (The athlete's heart):

- **Definition:** a variety of physiological, morphological and ECG changes that develop due to endurance (dynamic or aerobic) or isometric (static) sports.
- **Physiological changes include:**
 - Increased stroke volume and cardiac output.
 - Increased arteriovenous oxygen difference.
 - Increased maximum oxygen consumption.
 - Reduced basal heart rate.
- **ECG changes include:**
 - Increased precordial voltages.
 - Q waves and repolarization abnormalities.

- Highly trained endurance athletes can have resting bradycardia, marked sinus arrhythmia, first degree heart block, Mobitz I second-degree AV block and even third-degree AV block during sleep. (Due to increased resting vagal tone and reduced sympathetic tone).
- The reduced AV conduction velocity may make accessory conduction pathways such as those of WPW syndrome, more apparent.
- The increased vagal tone may also contribute to an increased prevalence of an early repolarization ST-segment pattern and ST-T changes in athletes.
- There is a misconception that inverted T waves in precordial leads are frequently encountered in trained athletes. T-wave inversion due to CV adaptation in an athlete should only be accepted once inherited and acquired form of CV disease have been definitely excluded.
- There is a U-shaped relationship between exercise training and AF (reduction in AF with moderate amount of physical activity and increase with low level and more intense and prolonged activity).
- **Morphological changes include:**
 - **Exercise-related acute cardiac findings:**

Cardiac fatigue: attenuated LV and RV EF immediately following ultraendurance exercise (ranging 50 to 160 km), with larger reductions on the RV. It typically manifests as increases in cardiac troponin and decreases in GLS and systolic twist.

Mechanisms of cardiac fatigue include: (1) decreases in blood volume may attenuate cardiac preload; (2) circulating catecholamines may decrease β -adrenoreceptor sensitivity; and (3) oxidative stress and/or cardiomyocyte membrane damage may attenuate ventricular function.
 - **Chronic cardiac exercise adaptation:**
 - Preserved systolic and diastolic functions.
 - **Ventricular and atrial chamber enlargement:** Ventricular dilation is common among athletes engaged in sports with a moderate-to-high dynamic component.

This may be accompanied by a mildly reduced LVEF (45-50%) in elite endurance athletes, which can complicate differentiation from dilated cardiomyopathy. Physiological LV dilation should be accompanied by balanced dilation of all cardiac chambers coupled with normal to supranormal LV diastolic function. Isolated LV dilation, reduced diastolic function, abnormal GLS (worse than -16%), regional wall motion abnormalities, and fibrosis by LGE on CMR are all supportive of cardiomyopathy.

RV dilation should be accompanied by concomitant 4-chamber enlargement; an enlarged RV in isolation is atypical and requires a complete work-up to differentiate from ARVC.

- **Increased LV mass and occasionally wall thickness:** About 2% of adult male athletes show mildly increased LV wall thickness of 13 to 15 mm where an overlap with mild forms of HCM can occur. The presence of substantial mitral valve SAM would confirm the diagnosis of HCM. The LVH of the athlete's heart is regarded as a benign adaptation to systematic training unassociated with adverse cardiovascular consequences. Cessation of exercise training or "deconditioning" may help in clinically differentiating adaptations to exercise training from HCM. Regression of eccentric LVH can occur in highly trained athletes after 6-34 weeks of abstinence from exercise.
- **Increased LV and RV trabeculations** occur in 20% of athletes and should not be confused with pathology, particularly in the setting of a normal ECG and normal systolic and diastolic function. It may be due to volume load, similar to pregnancy.
- Long-term endurance athletes have **increased coronary artery calcification** scores. The significance of this finding is unknown and may be protective as densely calcified plaques are less likely to rupture.
- **Causes of sudden cardiac death in athletes:**
 - In young athletes (< 35 years), sudden cardiac death occurs in about 1: 200,000 per year, but in older athletes (> 35 years), the incidence is somewhat higher at 1: 15,000 to 1: 50,000 per year.
 - In most athletes, cardiac arrest results from electrical instability and primary VAs. The major exception is Marfan syndrome, in which death usually results from aortic dissection or rupture.
 - In young athletes (< 35 years), causes of sudden cardiac death include:
 - Hypertrophic cardiomyopathy (commonest).
 - Congenital coronary artery anomalies (most often origin of left main coronary artery from the right sinus of Valsalva).

- Valvular heart disease (aortic stenosis, mitral valve prolapse).
- Dilated cardiomyopathy.
- Arrhythmogenic right ventricular cardiomyopathy
- Myocarditis.
- Marfan syndrome.
- Premature coronary atherosclerosis.
- Long QT syndrome.
- Brugada syndrome.
- Wolff-Parkinson-White syndrome.
- Catecholaminergic polymorphic ventricular tachycardia.
- Idiopathic ventricular tachycardia.
- Arrhythmias due to substance abuse with cocaine, anabolic steroids or ephedrine-containing compounds.
- In older athletes (> 35 years), sudden cardiac death may occur as a result of:
 - Coronary atherosclerosis (80% of all SCD in this population).
 - Hypertrophic cardiomyopathy.
 - Valvular heart disease
- **Commotio cordis:**
 - This condition refers to instantaneous cardiac arrest that results from a relatively modest non-penetrating blunt blow to the chest in the absence of underlying cardiovascular disease or injury to the chest wall or to the heart.
 - It occurs most commonly in children (mean age 13 years) with blunt precordial impact usually produced by a projectile (e.g. a baseball) or bodily collision with another athlete.
 - A precordial blow can create devastating electrophysiological consequences largely by virtue of its precise timing and location over the heart. Low energy chest impact during a very narrow window of 15-30 ms before the peak of the T wave results in VF, but when the precordium is struck during the QRS complex, transient complete heart block often occurs.

○ **Exercise-related acute MI:**

- Vigorous physical activity, generally defined as ≥ 6 METs (1 MET= 3.5 ml O₂/kg/min) of energy expenditure, transiently increase the risk for acute MI. This is predominantly due to: **(i)** acute coronary plaque disruption (secondary to increased flexing and banding of atherosclerotic coronary arteries during exercise) and, **(ii)** increased myocardial oxygen requirements (produced by increase in heart rate and systolic blood pressure).
- It should be noted that an increase of CK-MB and cTnT occurs in athletes following prolonged exertion and even after a brief intense treadmill run lasting only 30 min. Therefore, the diagnosis of acute cardiac event requires confirmation by ECG or imaging modalities.

| Table 34-1: Echocardiographic differentiation between HCM and Athlete heart: | | |
|---|------------|------------------------|
| Echo criteria | HCM | Athlete's heart |
| Atypical patterns of LVH | + | - |
| LVH regression after deconditioning | - | ++ |
| Small LV cavity (< 45 mm) | + | - |
| Big LV cavity (> 55 mm) | - | + |
| RV hypertrophy (RV free wall subcostal thickness > 5 mm) | + | - |
| LA dilatation (> 45 mm or ≥ 34 ml/m ²) | + | - |
| MV apparatus abnormalities | + | - |
| MR > mild | + | - |
| Dynamic obstruction (> 30 mmHg) | + | - |
| LV subendocardial systolic dysfunction | + | - |
| Pulsed DMI: $s' < 9$ cm/s; 2S-STE peak regional strain $\leq -15\%$ | | |
| Abnormal global diastolic function: Impaired LV relaxation | + | - |

| | | |
|---|---|---|
| LV subendocardial diastolic dysfunction Pulsed DMI: $e' < 7$ cm/s; $e'/a' < 1$ in any site | + | - |
| Delayed LV untwist (LV untwist extending > 25% of diastole) | + | - |

Exercise Prescription components:

When providing advice regarding an exercise programme or sports participation, the physician should indicate: **(i)** the type of sport; **(ii)** frequency and duration of the exercise programme; and **(iii)** the intensity that appears most appropriate to the individual.

- **Regarding to the type:** Exercise can be classified in different ways:

- **Strength related classification:**

- Endurance activities requiring regular contraction of large muscle groups and characterized by the relative percentage of maximal aerobic power (maximal oxygen uptake) required to perform that activity.
- Resistance “strength” activities requiring sustained muscle contractions performed to overcome resistance and can be characterized by the relative percentage of a maximal voluntary contraction.

- **Metabolically related classification:**

- Aerobic exercise refers to activity performed at an intensity that allows metabolism of stored energy to occur mainly through aerobic glycolysis and involves large muscle groups performing dynamic activities. Examples include cycling, running, and swimming performed at low to moderate intensity ⁽¹⁾.
- Anaerobic exercise refers to movement performed at high intensity unsustainable by oxygen delivery alone and requiring metabolism of stored energy to be processed largely by anaerobic glycolysis. Examples include weight training or intermittent high intensity exercise.

(1) Aerobic exercise training can either be continuous or interval based. The interval design involves the completion of short bouts of exercise at high intensities, interspersed with recovery periods. When compared with continuous training, this approach provides a greater challenge to the cardiopulmonary, peripheral, and metabolic systems and results in a more efficient training effect.

- **Related to the muscular work:**

- Isotonic (dynamic): contraction against resistance in which the length of the muscle shortens (concentric) or lengthens (eccentric).
- Isometric (static): contraction without change in length of the muscle.

- **Regarding to the frequency:** Exercise frequency is usually expressed as the number of times an individual engages in exercise per week. ESC guidelines recommend that healthy adults of all ages should perform a minimum of 150 min of moderate intensity endurance exercise training over 5 days or 75 min of vigorous exercise per week over 3 days, with additional benefit derived by doubling the amount to 300 min of moderate-intensity or 150 min of vigorous-intensity aerobic physical activity per week.

- **Regarding to the intensity:**

- Of all the basic elements of exercise prescription, exercise intensity is generally considered to be the most critical for achieving aerobic fitness and to have the most favourable impact on risk factors.
- Exercise intensity can be measured in absolute terms as the rate of energy expenditure during exercise (usually expressed in metabolic equivalents or kilocalories) or in relative terms.

Relative exercise intensity refers to a fraction of an individual's maximal power (load) that is maintained during exercise and is usually prescribed on the basis of a CPET.

The exercise test permits the formulation of the appropriate exercise prescription based on well-recognized indices including:

(i) percentage of maximal aerobic capacity (VO_{2max}), or **(ii)** a percentage of maximal heart rate (HR_{max}) recorded during an exercise test, or **(iii)** a percentage of a person's HR reserve (HRR), which uses a percentage of the difference between HR_{max} and resting HR and adds it to the resting HR (Karvonen formula), or **(iv)** the rate of perceived exertion (RPE) using borg scale ⁽¹⁾ or 'talk test', e.g. 'to be able to talk while exercising'.

(1) *The Borg Rating of Perceived Exertion (RPE) is a way of measuring physical activity intensity level. It is based on the physical sensations a person experiences during physical activity, including increased heart rate, increased respiration or breathing rate, increased sweating, and muscle fatigue. Your exertion rating based on a 6 to 20 rating scale. These include a rating of 6 perceiving "no exertion at all" to 20 perceiving a "maximal exertion" of effort.*

Based on the exercise testing results, the physician may indicate the intensity, mode, and duration of exercise that appears most suitable to the individual patient.

Table 34-2: Indices of exercise intensity for endurance sports from maximal exercise testing and training zones:

| Intensity | VO ₂ max (%) | HR _{max} (%) | HRR (%) | Borg RPE scale | Training zone |
|----------------------------|-------------------------|-----------------------|---------|----------------|-------------------------------------|
| Low intensity | < 40 | < 55 | < 40 | 10-11 | <i>Aerobic</i> |
| Moderate intensity | 40-69 | 55-74 | 40-69 | 12-13 | <i>Aerobic</i> |
| High intensity | 70-85 | 75-90 | 70-85 | 14-16 | <i>Aerobic + lactate</i> |
| Very high intense exercise | > 85 | > 90 | > 85 | 17-19 | <i>Aerobic + lactate + Anaerobe</i> |

- The intensity of resistance exercise is typically prescribed in terms of one repetition maximum (1 RM). One RM is defined as the maximum amount of weight a person can lift throughout a range of motion with one repetition. For convenience and compliance reasons the use of multiple (usually five) repetitions (5 RM) is suggested. Therefore, for power sports or resistance training, additionally maximal muscular testing is warranted in order to determine 1 RM or 5 RM.



Figure 34-1: Sporting discipline in relation to the predominant component (skill, power, mixed, and endurance) and intensity of exercise. Intensity of exercise must be individualized after maximal exercise testing, field testing and/or after muscular strength testing. **Source:** 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.

Exercise recommendations in individuals with CV risk factors:

- **General Recommendations:**

- Regular exercise reduces the risk of many adverse health outcomes irrespective of age, sex, ethnicity, or the presence of comorbidities. Indeed, there is a dose effect relationship between exercise and CV and all-cause mortality, with a 20-30% reduction in adverse events compared with sedentary individuals. Consequently, ESC guidelines recommend that healthy

adults of all ages should perform a minimum of 150 min of moderate intensity endurance exercise training over 5 days or 75 min of vigorous exercise per week over 3 days, with additional benefit derived by doubling the amount to 300 min of moderate-intensity or 150 min of vigorous-intensity aerobic physical activity per week.

- While exercise is also beneficial in patients with established CVD, the risk associated with vigorous exercise and sports in these individuals is increased. Importantly, CVD may be subclinical and unrecognized; therefore, consideration should be given to pre-participation assessment of risk in individuals with a higher likelihood of CVD.

Assessment of the individual likelihood of subclinical CVD may be performed by calculating the accumulated risk through established risk scores such as the SCORE risk charts and considering individual risk factors such as very high total cholesterol and LDL, DM, or a strong family history of CVD.

| Table 34-3: Ten-year cardiovascular risk categories (Systemic COronary Risk Evauation system; SCORE): | | |
|---|------|--|
| Very high risk | high | People with any of the following: <ul style="list-style-type: none"> ○ Documented ASCVD either clinical or unequivocal on imaging ⁽¹⁾. ○ Diabetes mellitus with target organ damage or at least three major risk factors or early onset of T1DM of long duration (> 20 years). ○ Severe CKD (eGFR < 30 ml/min/1.73m²) ○ A calculated 10-year SCORE of ≥ 10% ○ Family history with ASCVD or with another major risk factor. |
| High risk | | People with any of the following: <ul style="list-style-type: none"> ○ Marked elevation of a single risk factor, particularly cholesterol > 310 mg/dl (8 mmol), LDL-C > 190 mg/dL (> 4.9 mmol/L) or grade 3 hypertension (BP ≥ 180/110 mmHg). ○ Patients with FH without other major risk factors. |

(1) Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events such as significant plaque on coronary angiography or CT scan, or on carotid ultrasound.

| | |
|----------------------|---|
| | <ul style="list-style-type: none"> ○ People with DM without target organ damage, with DM duration ≥ 10 years or another additional risk factor. ○ Moderate CKD (eGFR 30-59 ml/min/1.73m²) ○ A calculated 10-year SCORE of 5-10% |
| Moderate risk | <p>People with any of the following:</p> <ul style="list-style-type: none"> ○ A calculated 10-year SCORE of 1-5% ○ Young patient (Patients with T1DM < 35 years, T2DM < 50 years) with duration < 10 years without other risk factors. |
| Low risk | People with calculated 10-year SCORE of < 1% |

- **Exercise management in individuals with CV risk factors:**

- **Obesity⁽¹⁾** : A pre-participation CV assessment is warranted in obese individuals who intend to engage in high-intensity exercise due to associated comorbidities such as type 2 DM, hypertension, dyslipidaemia, and CV and respiratory diseases. Obese individuals with a normal CV assessment should not have any restrictions on exercise. It may be reasonable to consider that obese individuals should limit high-volume weight-bearing exercises on a hard surface (i.e. < 2 h/day) until a considerable reduction in body weight is achieved (to avoid musculoskeletal injuries). Moreover, if high-volume exercise (> 2 h/day) is desired, a sufficient recovery time should be allowed for between periods of exercise (optimally 48 h).

- **Hypertension:**

Regular exercise intervention is associated with a mean reduction in SBP of 7 mmHg and DBP of 5 mmHg. Additional resistance training is highly effective in reducing BP further.

If high-intensity sports participation is desired, a pre-participation CV assessment is warranted to identify athletes with exercise-induced symptoms, excessive BP response to exercise, and the presence of end organ damage. If arterial hypertension is poorly controlled (resting SBP > 160 mmHg), a maximal exercise test should be postponed until the BP is controlled.

(1) **Obesity** is defined as BMI ≥ 30 kg/m² or (preferentially) a waist circumference > 80 cm for females or > 94 cm for males.

It is important to consider that beta-blockers are prohibited in certain competitive skill sports such as shooting. Diuretics are prohibited in all competitive sports. ACEIs, ARBs, and CCBs are the preferred drugs of choice in exercising individuals.

During sports participation, regular follow-up is recommended depending on the severity of hypertension and the category of risk. An exaggerated BP response to exercise increases the risk for incident hypertension in highly trained and normotensive athletes over a middle-term period. If SBP rise to >200 mmHg at a workload of 100 W during exercise testing, antihypertensive medical therapy should be optimized and clinical evaluation, including ECG and echocardiography, should be considered, even if the athlete is normotensive at rest.

- **Dyslipidemia:** Physical activity has favourable effects on lipid metabolism by reducing serum triglycerides by up to 50%, increasing HDL-C by 5-10%, and reducing LDL-C by up to 5%. These metabolic improvements can be achieved through 30-60 min of exercise on most days. Pharmacological intervention, particularly with statins, is superior to exercise and lifestyle intervention alone for reducing LDL-C and improving prognosis.
- **Diabetes mellitus:** The risk of developing T2DM is 50-80% higher in individuals who are physically inactive compared to their active counterparts. Aerobic exercise in patients with T2DM improves glycaemic control and reduces visceral fat and insulin resistance.

Individuals with diabetes have a higher likelihood of subclinical CAD; therefore, all individuals with diabetes should undergo CV assessment before taking up an exercise programme of high intensity. This should be supplemented by evaluation of glycaemic status, including risk factors for hypoglycaemia, history of hypoglycaemic episodes, presence of autonomic neuropathy, and antidiabetic treatment.

Asymptomatic individuals with DM and a normal CV assessment and maximal exercise test may engage in all sports but should be warned about the potential risk of iatrogenic hypoglycaemia in the event of inadequate caloric intake.

- **Exercise management in Elderly:**

- The elderly are defined as adults aged > 65 years. Similar to the general population, higher exercise capacity in this age group is associated with reduced mortality. Exercise helps to preserve neuromuscular competence, thus maintaining balance and coordination, which reduces the risk of falling.

- Moderate-intensity exercise is generally safe for older healthy people. The general recommendation for exercise implementation for the general population also applies to healthy elderly people.
- Elderly people should perform endurance and strength exercise, and specific exercises for flexibility and balance. Endurance exercise exerts beneficial effects on the cardiorespiratory system and resistance exercise prevents the decrease in muscle mass and sarcopenia.
- Potential risks for older people during exercise:
 - Arrhythmia, increase in BP, myocardial ischemia.
 - Musculoskeletal injuries and fractures.
 - Muscle soreness or swollen joints.
 - Increased risk of falls and subsequent injuries.

| Table 34-4: ESC recommendations for exercise and sports in healthy individuals: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| General recommendations: | | |
| <i>At least 150 min/week of moderate-intensity, or 75 min/week of vigorous-intensity aerobic exercise, or an equivalent combination thereof is recommended in all healthy adults.</i> | I | A |
| <i>A gradual increase in aerobic exercise to 300 min/week of moderate-intensity, or 150 min/week of vigorous-intensity aerobic exercise, or an equivalent combination is recommended for additional benefits in healthy adults.</i> | I | A |
| <i>Regular assessment and counselling to promote adherence and, if necessary, to support an increase in exercise volume over time are recommended.</i> | I | B |
| <i>Multiple sessions of exercise spread throughout the week, i.e., on 4-5 days a week and preferably every day of the week, are recommended.</i> | I | B |
| CV evaluation and regular exercise in healthy individuals > 35 years: | | |

| | | |
|--|------------|----------|
| <i>Among individuals with low to moderate CVD risk, the participation in all recreational sports should be considered without further CV evaluation.</i> | IIa | C |
| <i>Cardiac screening with family history, symptoms, physical examination, and 12-lead resting ECG should be considered for competitive athletes.</i> | IIa | C |
| <i>Clinical evaluation, including maximal exercise testing, should be considered for prognostic purposes ⁽¹⁾ in sedentary people and individuals with high or very high CV risk who intend to engage in intensive exercise programmes or competitive sports.</i> | IIa | C |
| <i>In selected individuals without known CAD who have very high CVD risk (e.g. SCORE > 10%, strong family history, or familial hypercholesterolemia) and want to engage in high- or very high-intensity exercise, risk assessment with a functional imaging test, coronary CCTA, or carotid or femoral artery ultrasound imaging may be considered.</i> | IIb | B |
| Special considerations for individuals with CV risk factors: | | |
| <i>In obese individuals <u>or</u> individuals with well-controlled hypertension <u>or</u> DM: resistance training ≥ 3 times per week, in addition to moderate or vigorous aerobic exercise (at least 30 min, 5-7 days per week) is recommended to reduce CVD risk.</i> | I | A |
| <i>Among adults with well-controlled hypertension but high risk and/or target organ damage, high-intensity resistance exercise is not recommended.</i> | III | C |
| <i>In individuals with uncontrolled hypertension (SBP > 160 mmHg), high-intensity exercise is not recommended until blood pressure has been controlled.</i> | III | C |
| Exercise in elderly patients: | | |
| <i>Among elderly adults (aged 65 years or older) who are fit and have no health conditions that limit their mobility, moderate-intensity aerobic exercise for at least 150 min/week is recommended.</i> | I | A |

(1) The aim of the exercise test is to identify prognostically important CAD and to assess the presence of exercise-induced arrhythmias.

| | | |
|---|------------|----------|
| <i>In older adults at risk of falls, strength training exercises to improve balance and coordination on at least 2 days a week are recommended.</i> | I | B |
| <i>A full clinical assessment including a maximal exercise test should be considered in sedentary adults aged 65 years or older who wish to participate in high-intensity activity.</i> | IIa | B |
| <i>Continuation of high- and very high-intensity activity, including competitive sports, may be considered in asymptomatic elderly athletes (master athletes) at low or moderate CV risk.</i> | IIb | C |

Exercise in patients with coronary artery disease:

Physical inactivity is a risk factor for CAD, but somewhat paradoxically, vigorous physical exertion transiently increases the risk for AMI and SCD. Atherosclerotic CAD is the predominant cause of exercise-related cardiac events (including ACS, AMI, and SCA) in individuals with established chronic coronary syndrome (CCS), **or** SCD as a primary presentation in individuals > 35 years of age. In addition to atherosclerotic CAD, other entities, including an anomalous origin of a coronary artery, myocardial bridge, and spontaneous coronary artery dissection (SCAD), are also associated with myocardial ischaemia, and potentially with Exercise-Related SCD.

▪ Individuals at risk of atherosclerotic CAD and asymptomatic individuals with CAD:

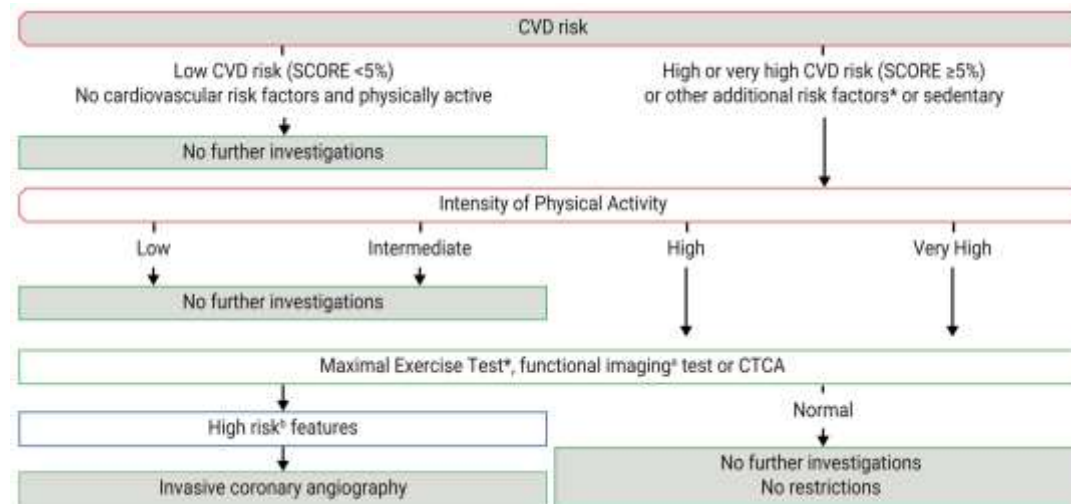


Figure 34-2: Proposed algorithm for CV assessment in asymptomatic individuals aged > 35-years-old with risk factors for CV disease and possible subclinical chronic coronary syndrome before engaging in sports. *Consider functional test or CCTA if exercise stress test is equivocal or the ECG is uninterpretable. **B) High risk* features:** SPECT: area of ischemia ≥ 10% of the LV myocardium; stress echocardiography: ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia; stress CMR: ≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments; CCTA: three-vessel disease with proximal stenoses; LM disease; proximal LAD disease. **Source:** 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.

Table 34-5: ESC Recommendations for exercise in individuals at risk of CAD or asymptomatic CAD detected at screening:

| Recommendations | Class | Level |
|--|------------|----------|
| <i>Among individuals with asymptomatic CCS (defined as CAD without inducible myocardial ischemia on a functional imaging or conventional exercise stress test), participation in all types of exercise, including competitive sports, should be considered based on individual assessment.</i> | Ila | C |

- **Established (long-standing) CCS:**

- All individuals with established CCS should be encouraged to perform the minimal physical activity recommendations for general and CV health. This applies to individuals with stable angina, asymptomatic and symptomatic individuals stabilized < 1 year after ACS, or individuals with recent revascularization, and asymptomatic and symptomatic individuals > 1 year after initial diagnosis or revascularization.
- Advice on intensive exercise and participation in most competitive sports in asymptomatic individuals with long-standing CCS should be based on several factors, which are determined through clinical history, exercise stress testing, or functional imaging and echocardiography.
- Individuals with high-risk coronary features may gradually return to sport 3-6 months after successful revascularization pending a normal maximal exercise or functional imaging test.
- Individuals taking dual antiplatelet agents should avoid sports with bodily collision, especially when they are combined with oral anticoagulants, due to the risk of haemorrhage.

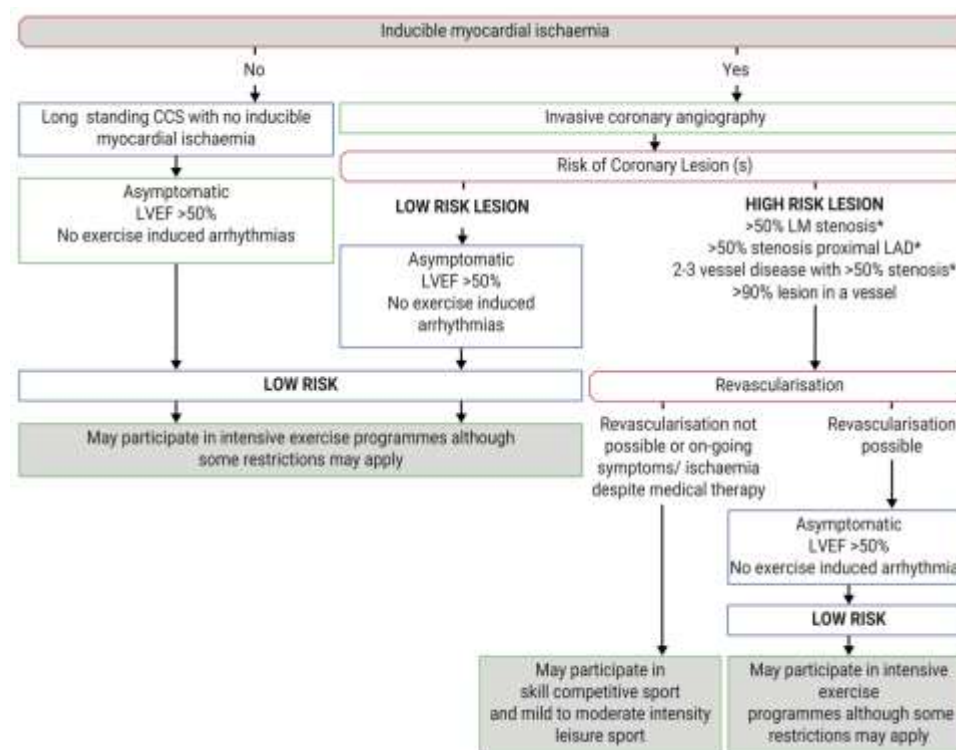


Figure 34-3: Clinical evaluation and recommendations for sports participation in individuals with established coronary artery disease. *With documented ischaemia or a haemodynamically relevant lesion defined by FFR < 0.8 or iFR < 0.9.
Source: 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.

Table 34-6: ESC Recommendations for exercise in individuals with long-standing chronic coronary syndrome:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Risk stratification for exercise-induced adverse events is recommended in individuals with established (long-standing) chronic coronary syndrome (CCS) prior to engaging in exercise.</i> | I | C |

| | | |
|--|------------|----------|
| <i>Regular follow-up and risk stratification of patients with CCS is recommended.</i> | I | B |
| <i>It is recommended that individuals at high risk of an adverse event from CAD are managed according to the current Guidelines on CCS.</i> | I | C |
| <i>Competitive or leisure sports activities (with some exceptions such as older athletes and sports with extreme CV demands) should be considered in individuals at low risk of exercise-induced adverse events.</i> | IIa | C |
| <i>Leisure-time exercise, below the angina and ischemic thresholds, may be considered in individuals at high risk of exercise-induced adverse events ⁽¹⁾, including those with persisting ischemia.</i> | IIb | C |
| <i>Competitive sports are not recommended in individuals at high risk of exercise-induced adverse events or those with residual ischemia, with the exception of individually recommended skill sports.</i> | III | C |

▪ **Return to sport after ACS:**

Exercise-based cardiac rehabilitation reduces cardiac mortality, hospital readmission, and anxiety. Individuals who have experienced an ACS, cardiac surgery, or percutaneous intervention should be referred to an early Exercise-based cardiac rehabilitation programme, soon after the discharge, for 8-12 weeks after the cardiac event.

Exercising individuals with CAD may start performing low- to moderate-intensity recreational sporting activities in parallel with participation in the structured progressive exercise programmes.

All types of sports activities may be considered, at an appropriate intensity level; however, careful attention should be paid to the development of new symptoms.

(1) High-risk features for exercise-induced adverse cardiac events in patients with atherosclerotic CAD include:

- Critical coronary stenosis > 70% in a major coronary artery or > 50% in the left main, and/or FFR < 0.8 and/or iFR < 0.9
- LVEF ≤ 50% and wall motion abnormalities
- Inducible myocardial ischemia on maximal exercise testing.
- NSVT, polymorphic or very infrequent ventricular premature beats, at rest and during maximal stress.
- Recent ACS ± PCI or surgical revascularization (< 12 months).

In general, structured outpatient exercise programmes, for 3-6 months, are required to achieve the appropriate level of activity for sports participation in patients with CAD. In individuals with NSTEMI or CCS who have had complete revascularization and do not have residual ischemia, exercise training can be progressed at a faster pace until the recommended exercise level is reached.

Competitive athletes:

In competitive athletes, an echocardiogram, maximal exercise test with 12-lead ECG recording or CPET is recommended for risk stratification before return to sports.

Recreational athletes:

In non-competitive, recreational sports, a symptom-limited/maximal exercise test should precede the return to sports. Higher-risk patients with CCS are not eligible for competitive sports; however, low-intensity skill sports, such as golf, may be considered, at intensities below the angina threshold.

If aerobic exercise is not tolerated, predominantly strength-related sports with a small amount of muscular work are recommended.

Table 34-7: ESC Recommendations for return to exercise after ACS:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Exercise-based cardiac rehabilitation is recommended in all individuals with CAD to reduce cardiac mortality and rehospitalization.</i> | I | A |
| <i>During the initial period, motivational and psychological support, and individualized recommendations on how to progress the amount and intensity of sports activities, should be considered in patients with CAD.</i> | Ila | B |
| <i>All sports activities should be considered, at an individually adapted intensity level in low-risk individuals with CCS.</i> | Ila | C |

▪ **Anomalous origin of coronary arteries (AOCA):**

- AOCA is a common cause of SCD in young athletes but is rarely implicated in individuals > 40 years of age.
- Chest pain, exertional syncope and SCD may be the first manifestation of AOCA.
- Ischemia may result from the compression of the anomalous vessel coursing between the aorta and the pulmonary artery and/or from the acute angled take-off from the aorta and/or the intramural course of the anomalous vessel.
- Both left and right anomalous coronary origins have been implicated in Exercise-related SCD, although the risk has been thought to be considerably higher with an anomalous left coronary artery origin.
- Exercise testing rarely reveals myocardial ischemia and CCTA, or CMR are the mainstay of diagnosis.

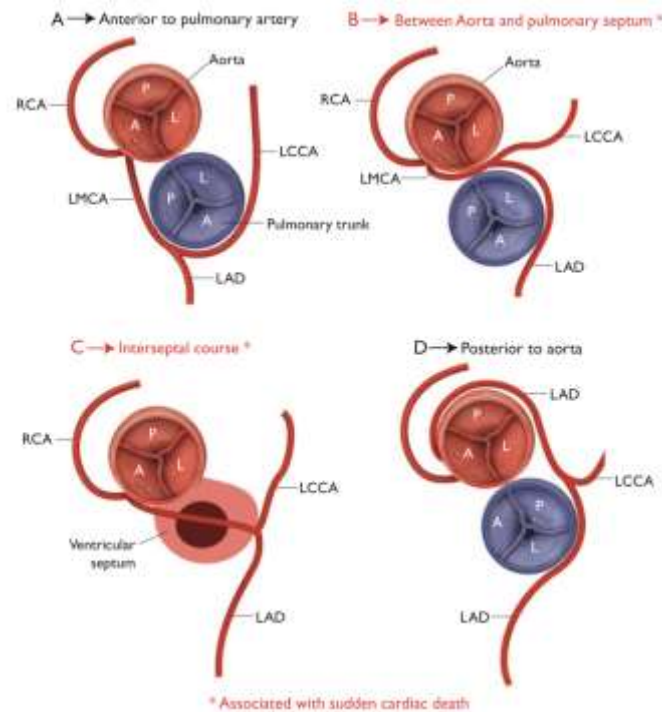


Figure 34-4: Schematic representation of the most frequent anomalous origin of coronary arteries and associated risk of SCD. Source: 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.

Table 34-8: ESC Recommendations for exercise in young individuals/athletes with anomalous origins of coronary arteries:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>When considering sports activities, evaluation with imaging tests to identify high-risk patterns and an exercise stress test to check for ischemia should be considered in individuals with AOCA.</i> | IIa | C |
| <i>In asymptomatic individuals with an anomalous coronary artery that does not course between the large vessels, does not have a slit-like orifice with reduced lumen and/or intramural course, competition may be considered, after adequate counselling on the risks, provided there is absence of inducible ischemia.</i> | IIb | C |
| <i>After surgical repair of an AOCA, participation in all sports may be considered, at the earliest 3 months after surgery, if they are asymptomatic and there is no evidence of inducible myocardial ischemia or complex cardiac arrhythmias during maximal exercise stress test.</i> | IIb | C |
| <i>Participation in most competitive sports with a moderate and high cardiovascular demand among individuals with AOCA with an acutely angled take-off or an anomalous course between the large vessels is not recommended. ⁽¹⁾</i> | III | C |

▪ **Myocardial bridging:**

| Table 34-9: ESC Recommendations for exercise/sports in individuals with myocardial bridging: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Participation in competitive and leisure-time sports should be considered in asymptomatic individuals with myocardial bridging and without inducible ischemia or ventricular arrhythmia during maximal exercise testing.</i> | IIa | C |

(1) This recommendation applies whether the anomaly is identified as a consequence of symptoms or discovered incidentally, and in individuals < 40 years of age.

Competitive sports are not recommended in individuals with myocardial bridging and persistent ischemia or complex cardiac arrhythmias during maximal exercise stress testing.

III

C

Exercise recommendations in individuals with chronic heart failure:

Exercise training studies in chronic heart failure have demonstrated a significant improvement in exercise tolerance and quality of life and a modest effect on all-cause and HF-specific mortality and hospitalization. Aerobic exercise is recommended for stable patients [NYHA class I-III], because of its well demonstrated efficacy and safety. Resistance exercise training may complement, but not substitute, aerobic exercise training because it reverses skeletal muscle mass loss and deconditioning without excessive stress on the heart. Recently, high-intensity interval training (HIIT) programmes have been considered as an alternative exercise modality for low-risk patients.

Key components before commencing an exercise programme and sports participation include:

- **Exclusion of contraindications to exercise:** e.g., hypotension or hypertension at rest or during exercise, unstable cardiac disease, deteriorating symptoms of HF, myocardial ischemia despite therapy (exercise may be permitted up to ischemic threshold), or severe and suboptimally treated pulmonary disease.
 - **Performing a baseline assessment:** including assessment of comorbidities and HF severity (e.g., by BNP and echocardiography). A maximal exercise test (preferably CPET) is important to assess functional capacity, exercise-induced arrhythmias or hemodynamic abnormalities and prescribe exercise intensity.
 - **Optimizing medical therapy:** All individuals with HF should be treated according to current HF guidelines.
-
- **Exercise in individuals with heart failure:**
 - Higher-risk patients including those who are suboptimally treated, those that remain in NYHA II or III despite optimal therapy, and those with exercise-induced arrhythmias or hypotension should not participate in competitive sports.

- Asymptomatic patients with HFrEF who are optimally treated may only be considered safe to perform specific low-intensity skill sports at a competitive level.
- Asymptomatic individuals with HFpEF or HFmrEF who are optimally treated may be eligible to participate in some competitive sports in the absence of exercise-induced arrhythmias or exercise-induced hypotension. In such cases, a progressive increase in exercise dose is recommended. Some restrictions may apply to high-intensity endurance, mixed and power sports with high demands, especially in older patients. No restrictions should apply for skill-related sports.
- Exercise-based cardiac rehabilitation programmes are a cornerstone in the prevention and management of HFpEF. Exercise intervention for 12-24 weeks increases functional capacity and quality of life.

• **Exercise in individuals after heart transplantation:**

Exercise reduces CV risk induced by post-transplantation immunosuppressive medical therapy, and increases physical performance, enabling heart transplantation (HTx) patients to achieve levels comparable to age-matched controls. HTx recipients participating in exercise-based cardiac rehabilitation programmes reveal a favourable outcome with respect to hospital readmission and longterm survival. Cardiac allograft neural reinnervation also contributes to improved functional capacity in the first year.

| Table 34-10: ESC Recommendations for participation in sports in heart failure | | |
|---|-------|-------|
| Recommendations | Class | Level |
| HF with reduced and mid-range EF: | | |
| <i>Before considering a sport activity, a preliminary optimization of heart failure risk factor control and therapy, including device implantation (if appropriate), is recommended.</i> | I | C |
| <i>Participation in sports activities should be considered in individuals with heart failure who are at low risk, based on a complete assessment and exclusion of all contraindications, in stable condition for at least 4 weeks, optimal treatment, and NYHA functional class I status.</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>Non-competitive (low- to moderate-intensity recreational) skill, power, mixed, or endurance sports may be considered in stable, asymptomatic, and optimally treated individuals with HFmrEF.</i> | IIb | C |
| <i>High-intensity recreational sports, adapted to the capabilities of the individual patient, may be considered in selected stable, asymptomatic, and optimally treated individuals with HFmrEF with an age-matched exercise capacity beyond average.</i> | IIb | C |
| <i>Non-competitive (low-intensity recreational skill-related sports) may be considered (when tolerated) in stable, optimally treated individuals with HFrEF.</i> | IIb | C |
| <i>High-intensity power and endurance sports are not recommended in patients with HFrEF irrespective of symptoms.</i> | III | C |
| HF with preserved EF: | | |
| <i>Moderate endurance and dynamic resistance exercise, together with lifestyle intervention and optimal treatment of CV risk factors (i.e., hypertension and type 2 DM) are recommended.</i> | I | C |
| <i>Competitive sports may be considered in selected stable patients without abnormalities on maximal exercise testing.</i> | IIb | C |
| Heart transplant recipients: | | |
| <i>Regular exercise through cardiac rehabilitation, combining moderate-intensity aerobic and resistance exercise, is recommended to revert pathophysiology to pre transplantation time, reduce CV risk induced by post-transplant medical treatment, and improve clinical outcome.</i> | I | B |
| <i>Recreational (low-intensity recreational) sports participation should be considered and encouraged in stable, asymptomatic individuals after therapy optimization.</i> | IIa | C |
| <i>Eligibility for competitive sports involving low and moderate-intensity exercise may be considered in selected, asymptomatic individuals with an uncomplicated follow-up.</i> | IIb | C |

Exercise recommendations in individuals with valvular heart disease:

- There is a theoretical possibility that a large stroke volume, coupled with vigorous mechanical contractions of the heart, and an increased chronotropic state induced by exercise may accelerate valve dysfunction. The ensuing effects on chronic stenotic or regurgitant lesions may cause compensatory cardiac hypertrophy, impaired ventricular function, myocardial ischaemia, cardiac arrhythmias, and possibly SCD.
- All individuals with valvular heart disease should be assessed with an exercise stress test to determine functional capacity and hemodynamic response and to exclude myocardial ischemia and complex arrhythmia prior to engaging in sport activity of moderate or high intensity.
- Asymptomatic individuals with mild to moderate valvular dysfunction who have preserved ventricular function and show good functional capacity without exercise-inducible myocardial ischaemia, abnormal haemodynamic response, or arrhythmias are considered “low risk” and may participate in all sports.
- Conversely, individuals with exertional symptoms, moderate or severe valvular dysfunction, left or right ventricular dysfunction, pulmonary hypertension, and exercise-induced cardiac arrhythmias or abnormal haemodynamic response are considered “high risk” and should be considered for invasive intervention.

▪ **Aortic Stenosis:**

| Table 34-11: ESC Recommendations for exercise and participation in recreational/competitive sports in asymptomatic patients with AS: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Mild AS: | | |
| Participation in all sports, if desired, is recommended. | I | C |
| Moderate AS: | | |

| | | |
|--|------------|----------|
| <i>Participation in all recreational sports involving low to moderate intensity, if desired, should be considered in individuals with LVEF \geq 50%, good functional capacity, and normal exercise test.</i> | IIa | C |
| <i>Participation in all competitive sports involving low to moderate effort, if desired, may be considered in individuals with LVEF \geq 50%, good functional capacity, and normal BP response during exercise.</i> | IIb | C |
| Severe AS: | | |
| <i>Participation in all sports/exercise involving low intensity, if desired, may be considered in individuals with LVEF \geq 50% and normal BP response during exercise.</i> | IIb | C |
| <i>Participation in sports/exercise of moderate and high intensity is not recommended.</i> | III | C |

▪ **Aortic regurgitation:**

| Table 34-12: ESC Recommendations for exercise and participation in recreational/competitive sports in asymptomatic patients with AR: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Mild AR: | | |
| <i>Participation in all sports, if desired, is recommended.</i> | I | C |
| Moderate AR: | | |
| <i>Participation in all sports, if desired, should be considered in asymptomatic individuals with a non-dilated LV with LVEF $>$ 50% and normal exercise stress test.</i> | IIa | C |
| Severe AR: | | |
| <i>Participation in all sports involving low and moderate intensity, if desired, may be considered with a mild or moderately dilated LV with LVEF $>$ 50% and normal exercise stress test.</i> | IIb | C |
| <i>Participation in any moderate- or high-intensity exercise is not recommended with LVEF \leq 50% and/or exercise-induced arrhythmias.</i> | III | C |

▪ **Bicuspid aortic valve:**

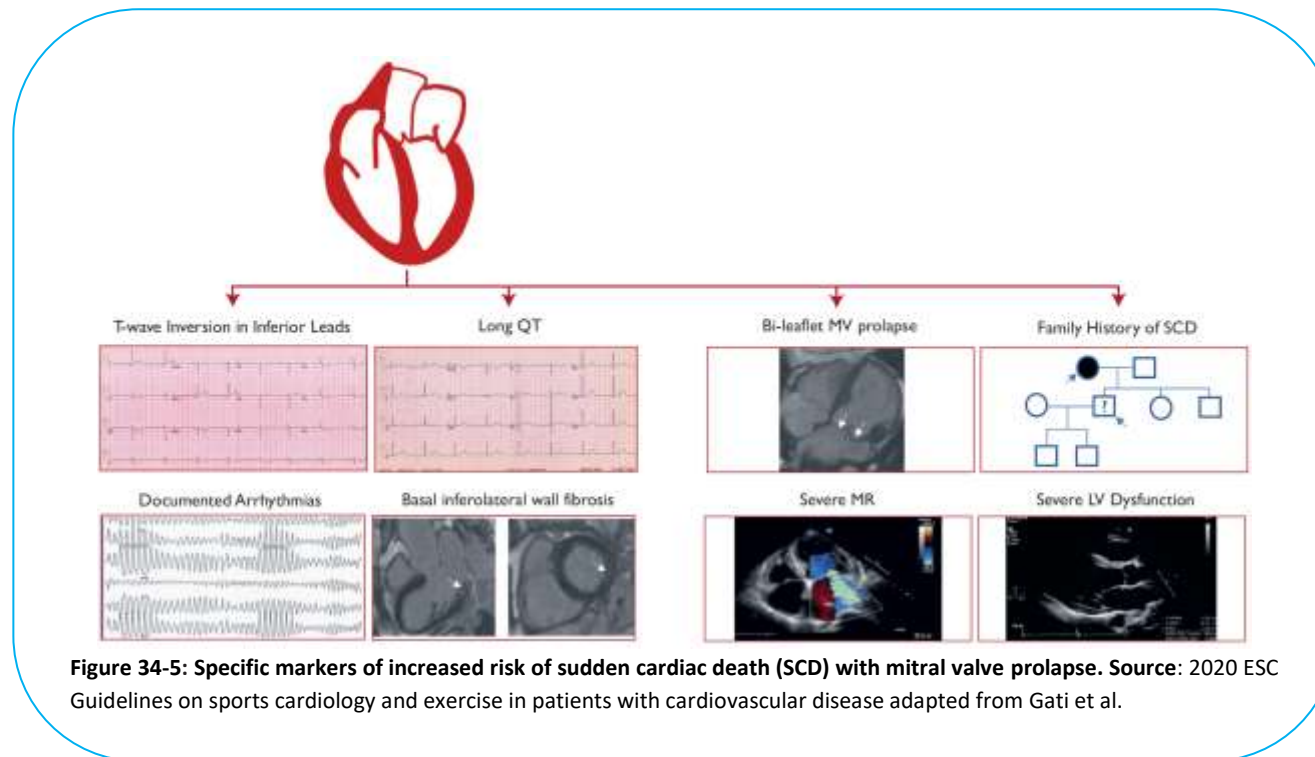
Currently, expert consensus panels advise a cautious approach to sports activities when the ascending aorta is above the normal limits. In the absence of aortopathy, exercise recommendations for individuals with BAV are identical to those in individuals with trileaflet aortic valve dysfunction.

▪ **Mitral Regurgitation:**

| Table 34-13: ESC Recommendations for exercise and participation in recreational/competitive sports in asymptomatic patients with MR: | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| Mild MR: | | |
| <i>Participation in all sports, if desired, is recommended.</i> | I | C |
| Moderate MR: | | |
| <i>Participation in all sports, if desired, should be considered in individuals fulfilling the following:</i> <ul style="list-style-type: none"> - LVEDD < 60 mm, or < 35.3 mm/m² in men and < 40 mm/m² in women - LVEF ≥ 60% - Resting sPAP < 50 mmHg - Normal exercise test | IIa | C |
| Severe MR: | | |
| <i>Participation in all sports involving low exercise intensity, if desired, may be considered in individuals fulfilling the following:</i> <ul style="list-style-type: none"> - LVEDD < 60 mm or < 35.3 mm/m² in men and < 40 mm/m² in women - LVEF ≥ 60% - Resting sPAP < 50 mmHg - Normal exercise test | IIb | C |

▪ **Mitral valve prolapse (MVP):**

- MVP is defined as > 2 mm displacement of one or both leaflets of the mitral valve beyond the annulus within the left atrium in end-systole. MVP is generally benign with a 10-year mortality risk of 5%.
- The most common complication of MVP is the progression to chronic severe MR, in 5-10% of individuals with MVP. Other complications include HF from chronic MR, pulmonary hypertension, infective endocarditis, supraventricular and VAs, and, occasionally, SCD.
- Individuals with MVP should be evaluated with an exercise test and 24-hour ECG.
- Given the relatively benign nature of MVP, asymptomatic patients with mild or moderate MR can participate in all competitive sports and leisure sports in the absence of the aforementioned risk factors.
- Asymptomatic patients with severe MR but none of the above high-risk markers may compete in low- to moderate-intensity sports after detailed discussion with their specialist.
- Symptomatic patients with MVP and any of the aforementioned high-risk features should not participate in recreational or competitive sports; however, low-intensity aerobic exercise should be encouraged to improve functional capacity and general well-being.



- **Mitral Stenosis:** No collision or body contact sports if anticoagulated for atrial fibrillation

| Table 34-14: ESC Recommendations for exercise and participation in recreational/competitive sports in asymptomatic patients with MS: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| Mild MS (MVA 1.5-2 cm ²): | | |
| Participation in all sports, if desired, is recommended in individuals with a resting sPAP < 40 mmHg and normal exercise test. | I | C |
| Moderate MS (MVA 1-1.5 cm ²): | | |

| | | |
|---|------------|----------|
| <i>Participation in all recreational sports involving low and moderate intensity, if desired, may be considered in individuals with resting sPAP < 40 mmHg and a normal exercise test.</i> | IIb | C |
| Severe MS (MVA < 1 cm²): | | |
| <i>Participation in leisure sports of moderate or high intensity is not recommended.</i> | III | C |
| <i>Participation in competitive sports is not recommended.</i> | III | C |

Exercise recommendations in individuals with aortopathy:

Most individuals with aortic pathology benefit from a certain minimal exercise programme and can at least participate in recreational sports. Because of the increase in BP and wall stress associated with intensive exercise and sports, such activities are potentially associated with an enhanced risk of aortic growth and also for acute aortic dissections or rupture.

Recommendations for exercise and sports should be individualized and based on the underlying diagnosis, the aortic diameter, family history for dissection or sudden death (risk factor), and the pre-existing fitness.

| Table 34-15: ESC Recommendations for exercise and participation in sports in individuals with aortic pathology: | | |
|---|--------------|--------------|
| Recommendations | Class | Level |
| <i>Prior to engaging in exercise, risk stratification, with careful assessment including advanced imaging of the aorta (CT/CMR) and exercise testing with BP assessment is recommended.</i> | I | C |
| <i>Regular follow-up including risk assessment is recommended.</i> | I | C |
| <i>Dynamic exercise should be considered more suitable than static exercise.</i> | IIa | C |
| <i>Participation in competitive or leisure-time sports activities (except power sports) should be considered in low-risk individuals.</i> | IIa | C |
| <i>Participation in individualized leisure exercise programmes may be considered in high-risk individuals.</i> | IIb | C |
| <i>Competitive sports are not recommended in individuals who are at high risk.</i> | III | C |

Table 34-16: Classification of risk to perform sports in patients with aortic pathology:

| | Low risk | Low-intermediate risk | Intermediate risk | High risk |
|------------------|---|---|--|---|
| Diagnosis | <ul style="list-style-type: none"> - Aorta < 40 mm in BAV, tricuspid valve - Turner syndrome without aortic dilatation | <ul style="list-style-type: none"> - MFS or other HTAD syndrome without aortic dilatation - Aorta 40-45 mm in BAV or tricuspid valve - After successful thoracic aorta surgery for BAV or other low risk situation | <ul style="list-style-type: none"> - Moderate aortic dilatation (40-45 mm in MFS or other HTAD; 45-50 mm in BAV or tricuspid valve, turner syndrome ASI 20-25 mm/m², TOF<50mm) - After successful thoracic aorta surgery for MFS or HTAD | <ul style="list-style-type: none"> - Severe aortic dilatation (> 45mm in MFS or other HTAD, > 50mm in BAV or tricuspid valve, turner syndrome ASI > 25 mm/m², TOF > 50 mm) - After surgery with sequelae |
| Advice | All sports permitted with preference for endurance over power sports. | <ul style="list-style-type: none"> - Avoid high and very high intensity exercise and power sports. - Preference of endurance over power sports | Only skill sports or mixed or endurance sports at low intensity | Sports are temporarily contraindicated. |
| Follow-up | Every 2-3 years | Every 1-2 years | Every 6 mon. to 1 year | Re-evaluation after treatment |

Exercise recommendations in cardiomyopathies:

▪ Hypertrophic cardiomyopathy:

| Table 34-17: ESC Recommendations for exercise and sports participation in individuals with HCM: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| Exercise recommendations: | | |
| Participation in high-intensity exercise/competitive sports, if desired (with the exception of those where occurrence of syncope may be associated with harm or death), may be considered for individuals who do not have any markers of increased risk ⁽¹⁾ following expert assessment. | IIb | C |
| Participation in low- or moderate-intensity recreational exercise, if desired, may be considered for individuals who have any markers of increased risk following expert assessment. | IIb | C |
| Participation in all competitive sports, if desired, may be considered for individuals who are gene positive for HCM but phenotype negative. | IIb | C |
| Participation in high-intensity exercise (including recreational and competitive sports) is not recommended for individuals who have ANY markers of increased risk | III | C |
| Follow-up and further considerations relating to risk: | | |
| Annual follow-up is recommended for individuals who exercise on a regular basis. | I | C |
| Six-monthly follow-up should be considered in adolescent individuals and young adults who are more vulnerable to exercise-related SCD | IIa | C |
| Annual assessment should be considered for genotype-positive/phenotype-negative individuals for phenotypic features and risk stratification purposes. | IIa | C |

▪ **Arrhythmogenic cardiomyopathy:**

(1) **Markers of increased risk:** (i) cardiac symptoms or history of cardiac arrest or unexplained syncope; (ii) moderate ESC risk score ($\geq 4\%$) at 5 years; (iii) LVOT gradient at rest > 30 mmHg; (iv) abnormal BP response to exercise; (v) exercise-induced arrhythmias.

Table 34-18: ESC Recommendations for exercise in individuals with arrhythmogenic cardiomyopathy

| Recommendations | Class | Level |
|---|--------------|--------------|
| Exercise recommendations: | | |
| <i>Participation in 150 min of low-intensity exercise per week should be considered for all individuals.</i> | IIa | C |
| <i>Participation in low- to moderate-intensity recreational exercise/sports, if desired, may be considered for individuals with no history of cardiac arrest/VA, unexplained syncope, minimal structural cardiac abnormalities, < 500 PVCs/24 h and no evidence of exercise-induced complex VAs.</i> | IIb | C |
| <i>Participation in high-intensity recreational exercise/sports or any competitive sports is not recommended in individuals with ACM, including those who are gene positive but phenotype negative.</i> | III | B |
| Follow-up and further considerations relating to risk: | | |
| <i>Annual follow-up is recommended for individuals who exercise on a regular basis.</i> | I | C |
| <i>Annual assessment should be considered for genotype-positive/phenotype-negative individuals for phenotypic features and risk stratification purposes.</i> | IIa | C |
| <i>Six-monthly follow-up should be considered in</i> <ul style="list-style-type: none"> <i>- adolescent individuals and young adults who are more vulnerable to exercise-related SCD.</i> <i>- individuals with high arrhythmic risk genotypes such as DSP, TMEM43, and carriers of multiple pathogenic variants.</i> | IIa | C |

▪ **Left ventricular non-compaction (LVNC):**

Table 34-19: ESC Recommendations for exercise in individuals with LV non-compaction cardiomyopathy

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>A diagnosis of LVNC in athletic individuals should be considered if they fulfil imaging criteria, in association with cardiac symptoms, family history of LVNC or cardiomyopathy, LV systolic (EF < 50%) or diastolic dysfunction ($e' < 9$ cm/s), a thin compacted epicardial layer (< 5 mm in end-diastole on CMR, or < 8 mm in systole on echocardiography), or abnormal 12-lead ECG.</i> | Ila | B |
| Exercise recommendations: | | |
| <i>Participation in high-intensity exercise and all competitive sports, if desired, with the exception where syncope may cause serious harm or death, may be considered in asymptomatic individuals with LVNC and LVEF $\geq 50\%$ and absence of frequent and/or complex VAs.</i> | Ilb | C |
| <i>Participation in recreational exercise programmes of low to moderate intensity, if desired, may be considered in individuals with LVEF 40-49% in the absence of syncope and frequent or complex VAs on ambulatory Holter monitoring or exercise testing.</i> | Ilb | C |
| <i>Participation in high- or very high-intensity exercise including competitive sports, if desired, may be considered for individuals who are gene positive for LVNC but phenotype negative (with the exception of lamin A/C or filamin C carriers).</i> | Ilb | C |
| <i>Participation in high-intensity exercise or competitive sports is not recommended in individuals with any of the following: symptoms, LVEF < 40% and/or frequent and/or complex VAs on ambulatory Holter monitoring or exercise testing.</i> | III | C |
| Follow-up and further considerations: | | |
| <i>Annual assessment for risk stratification is recommended for individuals with LVNC and genotype positive/phenotype-negative individuals who exercise on a regular basis</i> | I | C |

▪ **Dilated cardiomyopathy:**

Table 34-20: ESC Recommendations for exercise in individuals with dilated cardiomyopathy:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Participation in low- to moderate-intensity recreational exercise should be considered in all individuals with DCM, regardless of the EF, in the absence of limiting symptoms, and exercise-induced VAs.</i> | Ila | C |
| <i>Participation in high- or very high-intensity exercise including competitive sports (with the exception of those where occurrence of syncope may be associated with harm or death) may be considered in asymptomatic individuals who fulfil all of the following: (i) mildly reduced LV systolic function (EF 45-50%); (ii) absence of frequent and/or complex VAs on ambulatory Holter monitoring or exercise testing; (iii) absence of LGE on CMR; (iv) ability to increase EF by 10-15% during exercise; and (v) no evidence of high-risk genotype (lamin A/C or filamin C).</i> | Ilb | C |
| <i>Participation in all competitive sports may be considered in individuals with DCM who are genotype positive and phenotype negative, with the exception of carriers of high-risk mutations (lamin A/C or filamin C).</i> | Ilb | C |
| <i>Participation in high- or very high-intensity exercise including competitive sports is not recommended for individuals with a DCM and any of the following: (i) symptoms or history of cardiac arrest or unexplained syncope; (ii) LVEF < 45%; (iii) frequent and/or complex VAs on ambulatory Holter monitoring or exercise testing; (iv) extensive LGE (>20%) on CMR; or (v) high-risk genotype (lamin A/C or filamin C).</i> | III | C |
| Follow-up recommendations: | | |
| <i>Annual follow-up is recommended for individuals with DCM who exercise on a regular basis.</i> | I | C |
| <i>Six-monthly follow-up should be considered in individuals with high-risk mutations and adolescent individuals and young adults whose DCM phenotype may still be evolving and who are more vulnerable to exercise-related SCD.</i> | Ila | C |

Annual assessment should be considered for genotype-positive/phenotype-negative individuals for phenotypic features and risk stratification purposes.

Ila

C

Exercise recommendations in myocarditis, and pericarditis:

▪ Myocarditis:

Table 34-21: ESC Recommendations for exercise in individuals with myocarditis:

| Recommendations | Class | Level |
|---|--------------|--------------|
| <i>Comprehensive evaluation, using imaging studies, exercise stress test and Holter monitoring, is recommended following recovery from acute myocarditis to assess the risk of exercise-related SCD.</i> | I | B |
| <i>Return to all forms of exercise including competitive sports should be considered after 3-6 months in asymptomatic individuals, with normal troponin and biomarkers of inflammation, normal LV systolic function on echocardiography and CMR, no evidence of ongoing inflammation or myocardial fibrosis on CMR, good functional capacity, and absence of frequent and/or complex VAs on ambulatory Holter monitoring or exercise testing.</i> | Ila | C |
| <i>Among individuals with a probable or definitive diagnosis of recent myocarditis, participation in leisure-time or competitive sports while active inflammation is present is not recommended.</i> | III | C |
| <i>Participation in moderate- to high-intensity exercise for a period of 3-6 months after acute myocarditis is not recommended.</i> | III | B |
| <i>Participation in leisure exercise or competitive sports involving high intensity in individuals with residual myocardial scar and persistent LV dysfunction is not recommended.</i> | III | C |

▪ Pericarditis:

| Table 34-22: ESC Recommendations for exercise in individuals with pericarditis: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>Return to all forms of exercise including competitive sports is recommended after 30 days to 3 months for individuals who have recovered completely from acute pericarditis, depending on clinical severity</i> | I | C |
| <i>Participation in leisure-time or competitive sports is not recommended for individuals with a probable or definitive diagnosis of recent pericarditis while active inflammation is present, regardless of age, sex, or extent of LV systolic dysfunction.</i> | III | C |
| <i>Participation in moderate- to high-intensity exercise, including competitive sports, is not recommended for individuals with constrictive pericarditis.</i> | III | C |

Exercise recommendations in arrhythmia and channelopathies:

▪ Atrial fibrillation:

| Table 34-23: ESC Recommendations for exercise in individuals with atrial fibrillation: | | |
|--|-------|-------|
| Recommendations | Class | Level |
| <i>Regular physical activity is recommended to prevent AF.</i> | I | A |
| <i>Evaluation and management of structural heart disease, thyroid dysfunction, alcohol or drug abuse, or other primary causes of AF is recommended before engaging in sports.</i> | I | A |
| <i>Counselling about the effect of long-lasting intense sports participation on (recurrence of) AF is recommended in individuals with AF who exercise vigorously for prolonged periods, especially in middle-aged men.</i> | I | B |

| | | |
|---|------------|----------|
| <i>AF ablation is recommended in exercising individuals with recurrent symptomatic AF, and/or in those who do not want drug therapy, given its impact on athletic performance.</i> | I | B |
| <i>The ventricular rate while exercising with AF should be considered in every exercising individual (by symptoms and/or by ECG monitoring), and titrated rate control should be instituted.</i> | IIa | C |
| <i>Participation in sports without antiarrhythmic therapy should be considered in individuals without structural heart disease, and in whom AF is well tolerated.</i> | IIa | C |
| <i>Cavo-tricuspid isthmus ablation should be considered in those with documented flutter who want to engage in intensive exercise, to prevent atrial flutter 1 : 1 AV conduction.</i> | IIa | C |
| <i>Prophylactic cavo-tricuspid isthmus ablation to prevent flutter should be considered in individuals with AF who want to engage in intensive exercise and in whom class I drug therapy is initiated.</i> | IIa | C |
| <i>The use of class I antiarrhythmic drugs as monotherapy, without proof of adequate rate control of AF/AFL during vigorous exercise, is not recommended.</i> | III | C |
| <i>After ingestion of pill-in-the-pocket flecainide or propafenone, participation in intensive sports is not recommended until two half-lives of the antiarrhythmic drug have elapsed (i.e. up to 2 days)</i> | III | C |
| <i>Sports with direct bodily contact or prone to trauma are not recommended in exercising individuals with AF who are anticoagulated.</i> | III | A |

▪ **Supraventricular tachycardia and Wolff-Parkinson White syndrome:**

| Table 34-24: ESC Recommendations for exercise and sports participation in individuals with paroxysmal SVT and pre-excitation: | | |
|--|---------------------|---------------------|
| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |

| | | |
|---|------------|----------|
| <i>In individuals with palpitations, a comprehensive assessment to exclude (latent) pre-excitation, structural heart disease, and VAs is recommended.</i> | I | B |
| <i>Participation in all sports activities is recommended in individuals PSVT without preexcitation.</i> | I | C |
| <i>Ablation of the accessory pathway is recommended in competitive and recreational athletes with pre-excitation and documented arrhythmias.</i> | I | C |
| <i>In competitive/professional athletes with asymptomatic pre-excitation, an EP study is recommended to evaluate the risk for sudden death.</i> | I | B |
| <i>In competitive athletes with PSVT but without pre-excitation, curative treatment by ablation should be considered.</i> | IIa | C |

▪ **PVCs and non-sustained VT:**

Table 34-25: ESC Recommendations for exercise in individuals with premature ventricular contractions or non-sustained ventricular tachycardia

| <i>Recommendations</i> | <i>Class</i> | <i>Level</i> |
|---|---------------------|---------------------|
| <i>In exercising individuals with ≥ 2 PVCs on a baseline ECG (or ≥ 1 PVC in the case of high-endurance athletes), a thorough evaluation (including detailed family history) to exclude underlying structural or arrhythmogenic conditions is recommended.</i> | I | C |
| <i>Among individuals with frequent PVCs and nonsustained VT, a thorough investigation with Holter monitoring, 12-lead ECG, exercise test, and suitable imaging is recommended.</i> | I | C |
| <i>It is recommended that all competitive and leisure-time sports activities are permitted, with periodic re-evaluation in individuals without familial or structural underlying disease.</i> | I | C |

▪ **Long QT syndrome:**

Table 34-26: ESC Recommendations for exercise in long QT syndrome:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>It is recommended that all exercising individuals with LQTS with prior symptoms or prolonged QTc be on therapy with beta-blockers at target dose.</i> | I | B |
| <i>It is recommended that exercising individuals with LQTS should avoid QT prolonging drugs and electrolyte imbalance such as hypokalemia and hypomagnesaemia.</i> | I | B |
| <i>Shared decision making should be considered regarding sports participation in patients with genotype-positive/phenotype-negative LQTS (i.e. < 470/480 ms in men/women). Type and setting of sports (individual vs. team), type of mutation, and extent of precautionary measures should be considered in this context.</i> | IIa | C |
| <i>Participation in high-intensity recreational and competitive sports, even when on beta-blockers, is not recommended in individuals with a QTc > 500 ms or a genetically confirmed LQTS with a QTc ≥ 470 ms in men or ≥ 480 ms in women.</i> | III | B |
| <i>Participation in competitive sports (with or without ICD) is not recommended in individuals with LQTS and prior cardiac arrest or arrhythmic syncope.</i> | III | C |

▪ **Brugada syndrome:**

| Table 34-27: ESC Recommendations for exercise in Brugada syndrome | | |
|--|--------------|--------------|
| Recommendations | Class | Level |
| <i>ICD implantation is recommended in patients with BrS with episodes of arrhythmic syncope and/or aborted SCD.</i> | I | C |
| <i>Following implantation of an ICD, resumption of leisure or competitive sports should be considered after shared decision making in individuals who have not experienced recurrent arrhythmias over 3 months after ICD implantation.</i> | IIa | C |

| | | |
|--|------------|----------|
| <i>In asymptomatic individuals with BrS, asymptomatic mutation carriers and asymptomatic athletes with only an inducible ECG pattern, participation in sports activities that are not associated with an increase in core temperature > 39 C (e.g. endurance events under extremely hot and/or humid conditions) may be considered.</i> | IIb | C |
| <i>Prescription of drugs that may aggravate BrS, electrolyte abnormalities, and sports practice that increases core temperature > 39 C are not recommended in individuals with overt BrS or phenotypically negative mutation carriers.</i> | III | C |

Exercise recommendations following device implantation:

- Patients with a PM may participate in competitive or recreational sports in the absence of structural or other heart disease for which exercise may be prohibited.
- Shared decision making is appropriate when deciding whether or not to continue sports and the level of participation with an ICD. However, three important considerations come into play:
 - If sport is contraindicated because it can contribute to the progression of the underlying disease (such as in arrhythmogenic cardiomyopathy or lamin A/C mutations), an ICD cannot be considered as a substitute for sports restriction.
 - ICD shocks in general, even when appropriate and safe, will have a psychological impact on the athlete.
 - Situations where loss of focus or loss of consciousness could cause harm to a third party or the athlete (such as in motor sports, diving, mountain climbing, even cycling) should be avoided.
- For all patients with cardiac devices (PM, CRT and ICD), sports activities associated with a risk of chest trauma should be avoided. Some sports such as soccer, basketball, baseball may be possible while wearing appropriate padding.
- It is noteworthy that sports with pronounced arm movements such as volleyball, basketball, tennis, golf and climbing may increase the risk for late lead damage due to subclavian crush (with insulation or conductor failure).

| Table 34-28: ESC Recommendations for exercise in individuals with pacemakers and ICDs: | | |
|---|-------|-------|
| Recommendations | Class | Level |
| <i>It is recommended that individuals with implanted devices with/without resynchronization and underlying disease follow the recommendations pertaining to the underlying disease.</i> | I | B |
| <i>Participation in sports and exercise (except collision sports) should be considered in individuals with pacemaker therapy who do not have pathological substrates for fatal arrhythmias.</i> | IIa | C |
| <i>Prevention of direct impact to the implanted device by adapting the site of lead and/or device implantation, padding, or restricting direct impact sports should be considered.</i> | IIa | C |
| <i>Holter recordings and device interrogation during and after resuming sports should be considered to allow appropriate tailoring of rate responsive pacing parameters, exclusion of myopotential or electromagnetic inhibition, and detection of VAs.</i> | IIa | C |
| <i>Shared decision making should be considered during decisions relating to continuation of intensive or competitive sports participation in individuals with an ICD, taking into account the effect of sports on the underlying substrate, the fact that intensive sports will trigger more appropriate and inappropriate shocks, the psychological impact of shocks on the athlete/patient, and the potential risk for third parties.</i> | IIa | C |
| <i>An ICD is not recommended as a substitute for disease-related recommendations when these mandate sports restrictions.</i> | III | C |

Exercise recommendations in adult congenital heart disease:

Table 34-29: ESC recommendations for exercise in individuals with congenital heart disease:

| Recommendations | Class | Level |
|--|--------------|--------------|
| <i>Participation in regular moderate exercise is recommended in all individuals with CHD.</i> | I | B |
| <i>A discussion on exercise participation and provision of an individualized exercise prescription is recommended at every CHD patient encounter.</i> | I | B |
| <i>Assessment for ventricular function, pulmonary artery pressure, aortic size, and arrhythmia risk is recommended in all athletes with CHD.</i> | I | C |
| <i>Competitive sports participation should be considered for CHD athletes in NYHA class I or II who are free from potentially serious arrhythmias after individual tailored evaluation and shared decision making.</i> | IIa | C |
| <i>Competitive sports are not recommended for individuals with CHD who are in NYHA class III-IV or with potentially serious arrhythmias.</i> | III | C |

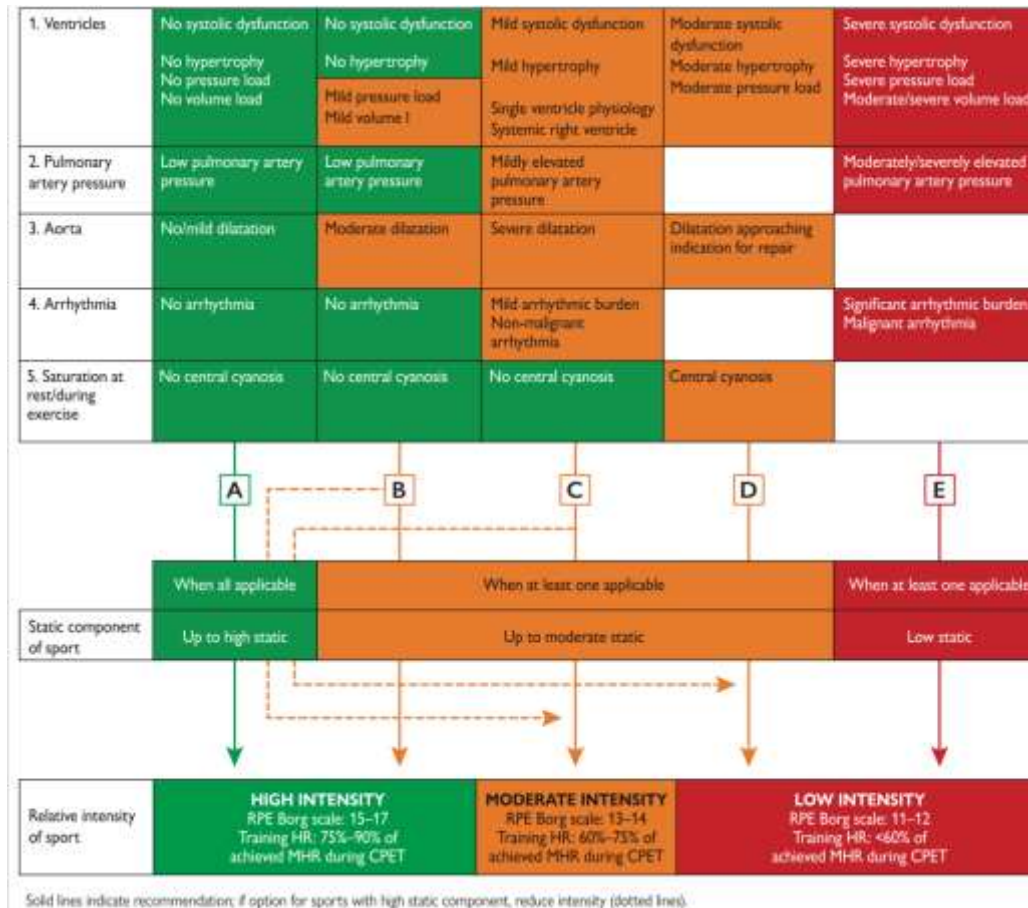


Figure 34-6: Pre-participation assessment of individuals with congenital heart disease. CPET = cardiopulmonary exercise test; HR = heart rate; MHR = maximum heart rate; RPE = rate of perceived exertion. AE represent pathways linking static and intensity components for each column. After assessment of CPET and the five variables, an individual recommendation can be given (solid arrow). If a higher static level sport is chosen, then a lower intensity level is advised (dotted arrow). **Source:** 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.

References and suggested readings:

- Antonio Pelliccia, Sanjay Sharma, Sabiha Gati, et al., ESC Scientific Document Group, 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC), *European Heart Journal*, Volume 42, Issue 1, 1 January 2021, Pages 17–96.
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Section

XI

Cardiac Involvement in Systemic Diseases

TO THE POINT

Chapter 35:

Cardiac Involvement in Systemic diseases

Shock

Definition:

Shock is defined as sustained SBP < 90 mmHg for at least 30 minutes, or the need for catecholamines to maintain SBP > 90 mmHg, *with* signs of low perfusion (oliguria < 30 ml/h, cold/clammy extremities, impaired mentation, increased lactate > 2 mmol/l).

Systemic pressure may be higher in shock patients with chronic hypertension; a decline in systolic pressure of > 40 mmHg is commonly used to define hypotension in the previously hypertensive patient.

Mechanisms:

There are four mechanisms of shock:

1. Hypovolemia.
2. Low cardiac output, as in left or right cardiogenic shock.
3. Vasodilatory shock, also called distributive shock (septic shock, anaphylactic shock, shock from excessive amount of sedatives and vasodilators).
4. Obstructive shock, where LV filling is prevented by a right-sided obstruction, such as pulmonary embolism, tamponade or isolated RV shock.

Right heart catheterization establishes the mechanism by assessing the three determinants of shock:

- Right- and left-sided filling pressures (CVP, PCWP). The normal CVP is <8–12mmHg.
- Cardiac output (CO). The normal cardiac index is 2.2–4.0 liters/min/m².
- Systemic vascular resistance (SVR). Normal SVR is 700–1500 dyn.s.cm⁻⁵.

Some shock states may be mixed:

- In septic shock, one may have a hypovolemic component and a cardiogenic component with reduced myocardial contractility, the so-called septic cardiomyopathy, seen in as many as 30% of cases.
- In septic shock, cardiac output needs to be high enough to match the increased tissue demands and the vasodilated circulation, and to compensate for the maldistribution of flow (skeletal muscle flow is increased, while splanchnic flow is reduced and heterogeneous because of microvascular congestion). A cardiac output that is “normal” in absolute values may be inappropriate in the context of septic shock; this is suggested when the tissue perfusion and SvO₂ are low (SvO₂ <65%) despite normalization of the systemic pressure.
- Both an adequate mean arterial pressure and an adequate cardiac output are required for end-organ perfusion.
- While cardiogenic shock is classically described in patients with acute large MIs, it is also seen in patients with chronic severe cardiomyopathy and decompensating factors, such as acute infection, tachyarrhythmia, excessive vasodilators or sedation, cases where the limited cardiac output reserve cannot match the dilated circulation.

N.B:

- ☞ In cardiogenic shock, SVR increases to maintain systemic pressure; SVR that is “normal” in value in the absence of vasodilator therapy is, in fact, relatively low.
- ☞ A shock state with a wide pulse pressure is characteristic of septic shock, AI, or any vasodilatory condition (cirrhosis, vasodilatory drug excess).
- ☞ Always remember adrenal shock (Addisonian shock), in which three mechanisms of shock are present (hypovolemia, low SVR, and myocardial depression). Importantly, functional adrenal failure may result from

septic shock. Also, think of adrenal shock in patients who are acutely sick and who have been receiving chronic steroid therapy; their chronically suppressed adrenal glands cannot generate stress doses of steroids.

| Table 35-1: Hemodynamic parameters in types of shock: | | | | |
|---|-----|------|--------------|-----|
| | CVP | PCWP | Cardic Index | SVR |
| Hypovolemic | ↓ | ↓ | ↓ | ↑ |
| Cardiogenic | ↑ | ↑ | ↓ | ↑ |
| Obstructive (543) | ↓ | ↓ | ↓ | ↑ |
| Distributive | ↓ | ↓ | ↓, N, ↑ | ↓ |

☞ SvO₂ is the mixed venous O₂ saturation, which is the O₂ saturation of the venous return, best sampled from the pulmonary artery (PA being the chamber where the venous blood achieves its best mixing from all sources). It may also be appropriately sampled from an SVC line.

It is the result of O₂ delivery to the tissues minus O₂ consumption by the tissues.

If O₂ delivery does not match O₂ demands, O₂ extraction will be high, which reduces the venous O₂ content and SvO₂. SvO₂ is thus a marker of how well O₂ delivery matches O₂ consumption, and a guide to appropriate shock therapy.

In the absence of anemia or hypoxemia, a low SvO₂ <60–65% implies that the cardiac output is inappropriate, even if high in absolute value.

Examples of O₂ delivery/consumption mismatch in different contexts:

(⁵⁴³) Disproportionately elevated PA pressure and CVP in comparison to PCWP suggest pulmonary embolism or precapillary pulmonary hypertension. In tamponade or isolated RV shock, equalization of CVP and PCWP is often seen.

- Septic shock: O₂ delivery is reduced from flow maldistribution and hypovolemia; O₂ demands are increased with requirements of a higher than normal O₂ delivery
- Reduced cardiac output, anemia, or hypoxemia reduces O₂ delivery.

Shock Management:

- **Goals of shock treatment:** Increase mean arterial pressure (MAP) to > 65 mmHg and provide good tissue perfusion, manifested as:
 - Urine output > 0.5 ml/kg/h, with a stable creatinine.
 - Absence of acidosis. Gastric PH or serum lactate may be monitored as a marker of perfusion.
 - Mixed venous O₂ saturation (SvO₂) ≥ 65–70%.
 - Heart rate < 120 bpm.
 - Warm skin with capillary refill ≤ 2 seconds.
- **Immediate management of any shock:** The shock and the volume status are quickly classified by history and physical exam, with a focus on:
 - Cardiac history.
 - Pulmonary edema, elevated JVP, and peripheral edema, which are signs of volume overload. Unlike pulmonary edema, peripheral edema does not necessarily preclude fluid resuscitation acutely in cases of septic or hemorrhagic shock.
 - Fever and potential sources of infection.
 - ECG and chest X-ray are quickly performed.
- **Intravenous fluid boluses:**
 - In the absence of pulmonary edema, a normal saline bolus of 0.5–2 liters is quickly administered in less than an hour (< 20 minutes for the first liter).

- Fluid administration is the first therapy of hypovolemic and low-SVR shocks; patients who have peripheral edema or elevated JVP are hypervolemic and are generally not fluid responsive.
- Fluids are administered until signs of fluid repletion develop. Alternatively, fluids may be administered until CVP is 8–12 mmHg (or 12–15mmHg in the case of ventilation with positive end-expiratory pressure) or PCWP is 15–18mmHg.
- In sepsis, colloid fluids have not been shown to be superior to crystalloid fluids (such as normal saline).
- If the patient remains hypotensive despite quick intravenous fluid resuscitation, especially if signs of fluid repletion develop (elevated JVP, pulmonary edema, decreased O₂ saturation):
- **Norepinephrine or dopamine** may be started (norepinephrine ≥ 0.05 mcg/kg/min, dopamine ≥ 3 mcg/kg/min). These two drugs are effective whether the shock is cardiogenic or distributive, until more is figured out.
- In a cardiogenic context, **inotropes** are administered: dobutamine is started at 3 mcg/kg/min if SBP > 80 mmHg, whereas dopamine or norepinephrine are started if SBP < 70–80mmHg. Dopamine may be administered at 3–10 mcg/kg/min (at this level, dopamine has mixed α +and β +effects, β +> α).
- In a septic context, **vasopressors** are administered: norepinephrine (mixed α +and β +effects, that is, vasoconstrictive and inotropic effects), phenylephrine (pure α +effect, without β +or inotropic effect), vasopressin.
- At this point, along with these initial measures:
- A central venous line may be placed to monitor CVP and help assess the volume status and SVO₂. A pulmonary artery catheter (Swan– Ganz) is not generally needed and has not been shown to improve outcomes in comparison to using a central line to measure CVP and SvO₂.
- An intra-arterial line is often necessary for blood pressure monitoring in any shock requiring inotropes and/or vasopressors.
- Echocardiography is performed.

- If the diagnosis remains in doubt and the patient does not improve despite the initial measures, a PA catheter may be placed to diagnose the mechanism of shock and to guide therapy.
- In the context of septic shock, if low perfusion signs persist despite achieving the target systemic pressure and despite a presumably normal volume status, consider that the cardiac output or the systemic pressure is still inadequate even if normal or high in absolute value. At this point, **inotropes** may be administered to increase cardiac output and O₂ delivery, allowing it to match the O₂ demands.
- Provide adequate oxygenation (arterial O₂ saturation >90–95%), and adequate hemoglobin level:
 - Intubate and mechanically ventilate in the case of any respiratory distress or obtundation. Respiratory effort can consume up to 30% of the cardiac output. Mechanical ventilation, by relieving the work of breathing, helps improve tissue perfusion.
 - In the absence of acute hemorrhage, red blood cells should only be transfused when hemoglobin decreases to <7–7.5 g/dl, with a target hemoglobin level of 7–9 g/dl.
- Perform a quick workup in parallel to the previous steps:
 - ECG, chest X-ray, cardiac enzymes, complete blood count, and blood/urine/sputum cultures are obtained.
 - Line infections are considered, and in case of doubt, lines older than 48 hours are removed and replaced. Infectious foci are sought (e.g., abdomen, joints, skin).
 - Bedside echocardiography is performed:
 - Echocardiography rules out tamponade, cardiogenic shock from LV failure, acute valvular disorders, and massive PE with acute RV failure.
 - Echocardiography helps determine:
 - RA, LA, and PA pressures, which help guide fluid therapy.
 - Volume responsiveness. A small LV cavity that is hypercontractile with near cavity obliteration or elevated LV outflow velocity often indicates hypovolemia.

- Start empiric broad-spectrum antibiotics whenever there is any suspicion of sepsis (start the antibiotics within 1 hour of this suspicion). Treat the potential source of infection (e.g., drain any abscess, remove central lines).
- Administer stress doses of steroids for a shock that persists for more than 1 hour despite inotropes/vasopressors or for the patient who uses steroids chronically
- In cardiogenic shock, look for a cause and treat it:
 - PCI+ IABP ± mechanical circulatory support (e.g., Impella) in MI.
 - Surgical correction of an acute valvular regurgitation or a mechanical complication of MI.
 - Cardioversion of a fast tachyarrhythmia (>150bpm).
 - Pacing for an inappropriately low heart rate, e.g., shock with a rate <60–70bpm.

A patient with shock is expected to be tachycardic. In fact, tachycardia attempts to compensate for an inappropriately reduced cardiac output. A “normal” heart rate of 50–70bpm is inappropriate in shock and may dictate temporary pacing.

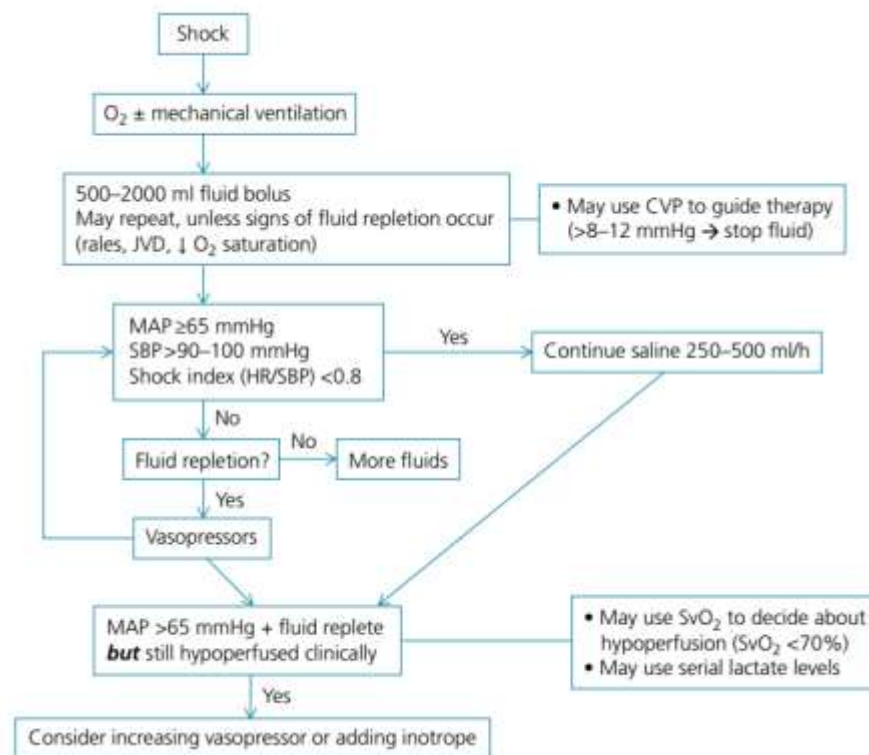


Figure 35-1: Aggressive early therapy of septic shock (the first 6 hours). Early goal-directed therapy implies the use of a central venous line with monitoring of CVP and SvO₂, but this is not necessary. Clinical signs of hypoperfusion consist of oliguria, serum lactate >4mmol/l, mottled skin. Effectiveness of therapy may be assessed by lactate clearance: a reduction of lactate levels ≥10% at 1–2-hour intervals suggests an improvement in tissue perfusion. **Source:** Hanna, E., 2017. *Practical cardiovascular medicine*. Chichester, West Sussex: Wiley Blackwell.

Fluid responsiveness:

Fluid responsiveness addresses the *improvement of cardiac output (> 10%) with fluid administration*.

- Passive leg raising-induced change in stroke volume, cardiac output, or pulse pressure reliably predicts volume responsiveness. An increase in cardiac output or stroke volume of > 12.5% or a change in pulse pressure of $\geq 9\%$ with passive leg raising suggests volume responsiveness. If a Swan–Ganz catheter is not in place, the change in stroke volume or cardiac output may be assessed using echocardiography. On echocardiography, stroke volume = (LVOT VTI \times LVOT area) or (aortic VTI \times aortic valve area).
- In any patient, whether spontaneously breathing or mechanically ventilated, a hyperdynamic LV with systolic cavity collapse or a hyperdynamic LV with intracavitary LV pressure gradient and SAM of the mitral valve implies severe hypovolemia, particularly hypovolemia associated with excessive use of inotropes. However, a small LV cavity may also be seen in overloaded patients with restrictive cardiomyopathy.
- **In spontaneously breathing patients:**

While the respiratory fluctuation in stroke volume and systolic arterial and pulse pressure may reflect hypovolemia (pulsus paradoxus), this is not sensitive or specific enough in patients who are spontaneously breathing. In such patients, rely on the clinical evidence of hypervolemia (peripheral edema), and assess the change in stroke volume or pulse pressure after passive leg raising or after a small volume load (500 ml). A decrease in CVP during inspiration may also predict fluid responsiveness (in severe RV failure, CVP increases with inspiration or remains unchanged rather than decreases).
- **In mechanically ventilated patients:**

Fluid responsiveness is better assessed using the dynamic response of stroke volume and systemic arterial waveform to positive pressure ventilation or to passive leg raising.

- During mechanical ventilation, the positive intrathoracic pressure reduces cardiac output in patients who are fluid-responsive, and analysis of the respiratory change in stroke volume or analysis of systemic arterial waveform from an arterial line is very helpful in addressing fluid responsiveness.
- Patients who are mechanically ventilated tend to have a larger IVC diameter and reduced IVC collapsibility because of the positive intrathoracic pressure that impedes venous return; that's why 12% collapsibility, as opposed to 50% in spontaneously breathing patients, is considered a sign of volume responsiveness.
- If the ventricles are on the steep portion of the Frank–Starling curve, an increase in venous return increases stroke volume, and thus the respiratory changes in venous return lead to respiratory fluctuations of the stroke volume. If the stroke volume varies by $> 20\%$ with respiration or if the systolic pressure or the pulse pressure decreases by $> 13\%$ between an end-expiratory hold and the next ventilatory cycle, the RV and the LV are sensitive to volume changes and are, therefore, volume-responsive.
- In mechanically ventilated patients who do not have an arterial line, the pulse oximetry tracing may be used to predict volume responsiveness. The plethysmographic waveform of pulse oximeters is a qualitative indicator of blood volume changes at the fingertip. However, the pulse oximetry tracing is not useful in hypotensive patients whose finger perfusion is reduced.

N.B:

☞ In chronic systolic HF, PCWP > 15 mmHg or CVP > 8 – 12 mmHg predicts the lack of fluid responsiveness; in diastolic HF or acute systolic HF, PCWP > 20 – 22 mmHg predicts the lack of fluid responsiveness. In fact, diuresis may improve cardiac output in these cases. However, while CVP and PCWP are helpful in establishing the mechanism of a shock, they only weakly predict fluid responsiveness, particularly when they are not severely reduced or severely elevated (e.g., CVP between 5 – 12 mmHg), or when the patient does not have an underlying systolic HF.

☞ **Peripheral edema that occurs after resuscitation means hypervolemia and signals the need to back off fluid resuscitation:** Contrary to common belief, the concept of “hypervolemia with intravascular volume depletion” is often untrue. Interstitial volume quickly equilibrates with plasma volume; therefore, edematous patients have excess of intravascular volume and are non-responsive to fluid administration.

Occasional exceptions are seen, such as at the onset of septic or hemorrhagic shock in a patient who previously had peripheral edema; because of the acute onset, the intravascular volume has not had time to equilibrate with the interstitial volume, and these patients are initially fluid-responsive despite hypervolemia. This may also occur in acute abdominal illnesses, cirrhosis with ascites, or immediately after abdominal surgery (when fluids tend to accumulate in the abdominal cavity).

☞ **SvO₂ vs. ScvO₂:**

Mixed central venous O₂ saturation (ScvO₂) represents SVC O₂ saturation and is normally lower than IVC O₂ saturation, which receives the high venous O₂ content of the renal veins (low renal O₂ extraction).

SVC O₂ is slightly lower than the overall mixed venous O₂ saturation (i.e. SvO₂). However, for patients in shock, a reversal of this relation occurs and ScvO₂ becomes greater than SvO₂ (by 5–10%).

Redistribution of blood away from the splenic, renal, and mesenteric blood (IVC territory) toward the cerebral circulation (SVC territory) leads to this phenomenon (more O₂ extraction in the IVC territory: SVC O₂ > IVC O₂ and PA O₂). In septic shock, the goal SvO₂ is > 65 % while the goal ScvO₂ is > 70 %.

Indications for transfusion:

Three classic randomized trials addressed transfusion in critically ill patients. All three trials showed that using a Hb transfusion cutoff < 7 g/dl, rather than 9 g/dl, is safe, and it was associated with a significant mortality reduction. Data on ACS patients are more sparse, but suggest that transfusion should be reserved for Hb < 8 g/dl, unless angina is ongoing.

The above thresholds apply to most patients. However, higher cutoffs (~9–9.5g/dl) should be used in patients with ongoing major bleed (e.g., hemorrhagic shock), and in those with severely symptomatic anemia, i.e., angina at rest/ischemia on ECG, angina or dyspnea on mild activity, or severe sinus tachycardia.

Conversely, fatigue is a vague symptom and is not, per se, a strong indication for transfusion.

Anemia is associated with worsened outcomes in all settings and may exacerbate myocardial ischemia in patients with CAD or ACS. Yet transfusion, by itself, does not always reverse this ischemia and leads to its own untoward effects. It increases volume overload in HF.

The transfused red cells are different from intrinsic red cells without as much capacity for O₂ carrying (the longer they are stored, the worse they get). Plus, transfused red cells have potential prothrombotic (ADP release) and proinflammatory effects.

In fact, while normal red blood cells transport and dispense nitric oxide to the microvasculature, this function is disrupted in transfused red blood cells, which leads to impaired regional vasodilatation.

General indications for transfusion in critically ill or ACS patients:

- In any critical illness, septic shock, or hemodynamically stable gastrointestinal bleed, a cutoff of 7–7.5g/dl is appropriate.
- In patients with active bleed and hemodynamic instability from bleeding, transfusion should be considered at a higher cutoff (9–9.5g/dl, even more sometimes)
- In patients with severe tachycardia, especially sinus tachycardia (>110–120bpm) that can only be attributed to anemia, transfusion may be considered at a higher cutoff (9g/dl)

- For ACS patients who are stabilized without angina, a Hb cutoff of 8g/dl is appropriate. If they continue to exhibit episodes of angina at rest or mild exertion, a higher cutoff may be used (likely 9–9.5g/dl). Also, in patients about to undergo PCI, a higher cutoff is generally used.
- In all patients, the cause of a new anemia should be sought and treated (bleeding, hemolysis). In ACS, this cause is sought before performing any PCI and before the administration of antithrombotic therapy.
For example, in a patient with Hb 8g/dl and severe angina: transfuse, perform endoscopy, start proton pump inhibitor, and ensure Hb stability for a few days before PCI.

Endocrine and Metabolic disorders

Acromegaly

Cardiac effects of the growth hormone:

- Increased myocardial contractility.
- Shift of myosin to the low ATPase activity V3 isoform.
- Increased heart rate.
- Induction of insulin resistance.

Cardiovascular manifestations of acromegaly:

- **Heart failure:** A specific acromegalic cardiomyopathy develops and progress in three stages: **(1)** hyperkinetic LV, **(2)** biventricular hypertrophy, diastolic filling abnormalities and impaired cardiac performance with exercise, **(3)** valvular disease (aortic and mitral regurgitation) and systolic and diastolic dysfunction with congestive heart failure.
Congestive HF may be resistant to treatment but improve with the administration of somatostatin analogues (octreotide, lanreotide) ⁽⁵⁴⁴⁾ or the growth hormone receptor antagonist (pegvisomant).
- **Hypertension** occurs in 25-40% of patients due to expansion of blood volume (secondary to insulin resistance), impairment of endothelial-dependent vasodilatation, decreased nitric oxide and increased sympathetic activity. It is usually mild and readily responsive to treatment (by sodium restriction and diuretics). Both ACEIs and ARBs cause a paradoxical increase in blood pressure.

⁽⁵⁴⁴⁾ Somatostatin is the hypothalamic hormone that reduces the secretion of growth hormone. Somatostatin infusion produces bradycardia as cardiac nerves contain somatostatin that regulates cardiac conduction.

- **ECG abnormalities** include left-axis deviation, septal Q waves, ST-T wave depression, abnormal QT dispersion and conduction defects.
- **Atrial and ventricular arrhythmias** and sudden death due to inflammatory and degenerative damage of the SAN and conduction tissue.
- **Derangements in cardiac autonomic function** as measured by heart rate recovery and variability.

Thyroid Disorders

Hemodynamic effects of thyroid hormone:

- Augmentation of LV systolic and diastolic functions.
- Decreased systemic vascular resistance by direct effect on smooth muscle cells and by increasing NO production.
- Increased plasma volume due to activation of renin-angiotensin-aldosterone system.
- Increased red cell mass due to increased erythropoietin production.
- Increased cardiac output. The combination of increased cardiac output and decreased systemic vascular resistance results in a wide pulse pressure.

Hyperthyroidism

Cardiovascular manifestations:

- Palpitation due to increased heart rate and contractility.
- Exertional dyspnea due to weakness of respiratory muscles.
- Exercise intolerance due to weakness of skeletal muscles.

- Clinical examination typically reveals hyperactive precordium, loud S1 and P2 as well as presence of S3 and occasionally a systolic ejection sound. Mid systolic murmurs along the left sternal border are common and a systolic scratch (Means-Lerman scratch) is occasionally heard in the 2nd left intercostal space during expiration. This scratch results from the rubbing of the pericardium against the pleura in the context of hyperdynamic circulation and tachycardia.
- Myocardial ischemia due to coronary spasm or associated coronary artery disease in older patients.
- Atrial fibrillation develops in up to 15% of patients. Nevertheless, the ability to restore the euthyroid state and sinus rhythm justifies TSH testing in most patients with a recent onset of AF or other SVT.
- Systolic hypertension is common and diastolic hypertension may also occur.
- Heart failure due to prolonged high heart rate resulting in hyperthyroid cardiomyopathy. Initially cardiac output is increased but later on it drops.
- Pulmonary hypertension due to increased cardiac output in absence of pulmonary vasodilatation (unlike the vasodilator response of the systemic circulation). All patients with unexplained pulmonary hypertension should be evaluated for thyroid disease by measurement of serum TSH.
- Graves disease may be associated with cerebrovascular ischemic symptoms in young patients due to occlusion of the terminal portion of the internal carotid arteries (moyamoya disease).
- Takotsubo cardiomyopathy may be a presenting manifestation of severe thyrotoxicosis.

Hypothyroidism

Cardiovascular manifestations:

- Sinus bradycardia.
- Pericardial effusion due to increased volume of distribution of albumin and a decrease in lymphatic clearance function. The effusion resolves with thyroid hormone replacement. Tamponade is rare.

- Hypertension particularly diastolic hypertension may occur in mild to moderate hypothyroidism, but patients with severe hypothyroidism are more likely to have normal or slightly low blood pressure.
- Increased risk for atherosclerotic coronary and systemic arterial disease due to combination of hypertension, increased LDL-C (decrease in LDL receptor number) and homocystein.
- Serum Creatine kinase (CK) may be elevated consistent with a skeletal muscle origin.
- ECG is characterized by sinus bradycardia, low voltage and prolonged QT interval.

Subclinical thyroid disease

- **Subclinical hyperthyroidism** is characterized by low serum TSH (< 0.1 mIU/ml) but normal T3 and T4 levels. It is associated with increased risk of total mortality and incidence of AF and heart failure. Therefore, treatment with methimazole may be considered. Cardio-selective beta blockers may improve the heart rate, LV mass and diastolic LV function.
- **Subclinical hypothyroidism** is characterized by elevated TSH ($> 3.5-4$ mIU/ml) but normal T3 and T4 levels. It is associated with high cholesterol levels, impaired LV diastolic function, endothelial dysfunction and increased risk of heart failure. Patients with TSH level $> 5-10$ mIU/L should be treated with levo-thyroxine 50-100 ug/day.

Parathyroid Disorders

Hyperparathyroidism: Cardiovascular manifestations:

- Impaired LV diastolic function in severe or chronic disease.
- Chronic hypercalcaemia increases calcium deposition in the fibrous skeleton of the heart, valvular cusps, coronary arteries and myocardial fibres. It may also accelerate atherosclerosis.
- ECG abnormalities: shortening of QT (hypercalcemia shortens phase 2 of the action potential), short PR intervals, conduction abnormalities, and ST-T wave changes suggestive of ischaemia.

Hypoparathyroidism: Cardiovascular manifestations:

- Dilated cardiomyopathy.
- ECG abnormalities: prolongation of QT (hypocalcemia prolongs phase 2 of the action potential).

Adrenal Insufficiency

Cardiovascular manifestations:

- Hypotension with postural accentuation.
- Reduced LV end-diastolic and end-systolic dimensions.
- ECG abnormalities: low voltage, sinus bradycardia, PR and QT prolongation and inverted T waves.

Primary aldosteronism

Aetiology:

The most common cause is aldosterone producing adenoma (Conn's syndrome), less commonly bilateral adrenal hyperplasia.

Other conditions include enzymatic deficiencies (11β -hydroxylase deficiency and 17α -hydroxylase deficiency) and chronic liquorice ingestion containing glycyrrhetic acid.

Clinical picture:

- Hypertension. In keeping with the profibrotic effect of aldosterone, many more CV events are seen in patients with primary aldosteronism than in patients with essential hypertension matched for age, gender and BP levels.
- Non-specific weakness, fatigue, polyuria, or cramps may be associated due to hypokalaemia.

Investigations:

- **Screening test:** Morning plasma Aldosterone : Renin ratio > 20 with plasma aldosterone concentration at least 12 ng/dl, should prompt confirmatory testing.
- **Confirmatory test:** Aldosterone suppression test in which the patient is given a high sodium diet for 3 days. A 24 hr urinary aldosterone excretion > 12 mcg/24 hr is diagnostic of aldosteronism.
- Imaging studies to detect adenoma include CT and MRI.
- Adrenal venous aldosterone levels should be measured when the biochemical findings are highly suggestive of an adenoma, but the adrenal CT or MRI is ambiguous.

Treatment:

- Medical therapy is indicated in patients with adrenal hyperplasia, bilateral adrenal adenomas and those who are poor surgical risks. A combination of a diuretic with either spironolactone 100-200 mg/d or eplerenone 50-100 mg/d corrects the hypokalaemia and hypertension within 2-4 weeks.
- Laparoscopic adrenalectomy is indicated for unilateral aldosterone producing adenomas.

Congenital adrenal hyperplasia

- Enzymatic defects may induce hypertension by interfering with cortisol biosynthesis. Low levels of cortisol lead to increased ACTH levels which increase the accumulation of precursors proximal to the site of enzymatic block, specifically, deoxycorticosterone which induces mineralocorticoid hypertension. The most common of such enzymatic defects are:
 - 11- β hydroxylase deficiency
 - 17- α hydroxylase deficiency

- Affected children are hypertensive and hypokalemic and may exhibit virilization (11- β hydroxylase deficiency) or failure of secondary sexual development (17- α hydroxylase deficiency).
- Corticosteroids are the mainstay of treatment.

Cushing syndrome

Aetiology:

Spontaneous Cushing's syndrome may be classified into:

- Corticotrophin-dependent: due to pituitary tumor (70-80%) or ectopic ACTH syndrome.
- Corticotrophin-independent: usually due to unilateral cortisol producing adenoma or carcinoma.

Clinical picture:

- Hypertension and hyperglycemia.
- Weight gain, central obesity, facial plethora, and hirsutism.
- Muscle wasting, osteoporosis, and easy bruising.
- Menstrual irregularities.

Investigations:

- **Initial screening test:** 24 h urinary free cortisol (UFC) or overnight dexamethasone suppression test.
The diagnosis is suggested if the 24 h UFC > 40 ug or serum cortisol > 5 g/dl in a blood sample withdrawn at 8:00 am after giving 1.0 mg of dexamethasone at 11:00 pm the night before. This should prompt measurement of plasma ACTH at 8:00 am.
- **Plasma ACTH:**

- A low plasma ACTH level is suggestive of an adrenal tumor or hyperplasia and should be evaluated further by abdominal CT.
- A high plasma ACTH level > 200 pg/ml is suggestive of ectopic ACTH-production and should prompt a search for ACTH-producing tumors such as small cell bronchial carcinoma or carcinoid tumors.
- A high plasma ACTH level but < 200 pg/ml suggests the diagnosis of either a pituitary tumor or ectopic ACTH production. Differentiation can be made by high-dose dexamethasone suppression test. It is done using a dose of 2.0 mg orally q 6h for 48h. A 24-h UFC and morning serum cortisol are measured at baseline and on the second day.
 - Suppression supports the diagnosis of pituitary tumor or hypothalamo-pituitary dysfunction.
 - Non-suppression is suggestive of ectopic ACTH production.
- A normal plasma ACTH level will require a corticotropin-releasing hormone (CRH) infusion test or metyrapone response test. Both tests demonstrate the responsiveness of the hypothalamo-pituitary axis in presence of cortisol excess:
 - An increase in plasma ACTH suggests a pituitary tumor or hypothalamo-pituitary dysfunction.
 - Lack of response suggests ectopic ACTH production.

Treatment:

- If a pituitary adenoma is responsible, it can be resected by transsphenoidal microsurgery.
- If an adrenal tumor is responsible, it should be removed surgically.
- Medical treatment for inoperable cases includes metyrapone, bromocriptine and ketoconazole.

Pheochromocytoma

- This is a catecholamine-producing tumor of the sympathoadrenal system. Nearly 80% of the tumors are limited to the adrenal gland, usually unilaterally. The tumors are likely to be bilateral or multiple in pediatric presentations or in familial forms such as neurofibromatosis, multiple endocrine neoplasia (MEN) types 2A or 2B and von-Hippel-Lindau disease.
- Most tumors secrete both norepinephrine and epinephrine although the former usually predominates. Other substances that may be secreted include calcitonin, vasoactive intestinal peptide, somatostatin, enkephalin, endorphins, serotonin and atrial natriuretic peptide.

Clinical picture:

- Patients usually present with clusters of symptoms that occur in paroxysms (spells). The three most common symptoms are headache, palpitation, and sweating. Many other symptoms may occur including anxiety, weakness and tremor. When norepinephrine is the primary hormone produced, pallor usually occurs but if substantial amounts of epinephrine are produced, flushing develops.
- Episodic hypertension develops as a result of catecholamine release from the tumor and the sympathetic nerves. Although some BP readings may be normal, most measurements are in the hypertension range but with wide variability.

Investigations:

- **Initial screening test:** 24 h urinary metanephrines.
- **If the urinary assays are borderline:** Plasma catecholamines (norepinephrine plus epinephrine):
 - If the levels > 2000 pg/ml in the basal state, the presence of pheochromocytoma is highly likely.
 - If the levels are < 600 pg/ml, the diagnosis is very unlikely.

- If the levels between 600 and 2000 pg/ml, the clonidine suppression test may be useful. The normal response to clonidine is suppression of plasma catecholamine level by at least 50% from baseline to below 500 pg/ml. Non-suppression of elevated plasma catecholamines by clonidine is strongly suggestive of pheochromocytoma.
- CT and MRI of the abdomen are used to localize the tumor after the diagnosis is established. If failed to localize the tumor, patients should have ¹³¹I metaiodobenzylguanidine (MIBG) total body scan to provide both anatomical localization and functional characterization of extra-adrenal pheochromocytomas and metastases.

Treatment:

- Pheochromocytomas should be resected. Endoscopic procedures are now the standard. Preoperative management usually includes several weeks of alpha blockers (especially phenoxybenzamine) and rehydration to avoid abrupt hypotension from withdrawal of the elevated catecholamines once the tumor pedicle is clamped. Beta-blockers can control arrhythmias during the perioperative period but should be administered only in conjunction with a-blockers to avoid unopposed alpha agonist influence. After tumor resection, patients should be followed up at least on annual basis to screen for recurrence or the development of a second pheochromocytoma.
- If the tumor is unresectable, chronic medical therapy can be used with the alpha blocker phenoxybenzamine or the inhibitor of catechol synthases α -methyl-tyrosine.

Rheumatic disorders

Rheumatoid arthritis

Cardiovascular manifestations:

- Cardiovascular disease is the most common cause of death in patients with rheumatoid arthritis. The prevalence of CV disease in rheumatoid arthritis is comparable to that of patients with DM.
- The pericardium is affected in about 50% of patients. Chronic asymptomatic effusion is more than acute pericarditis. Aspiration of pericardial effusion is not usually required. Constrictive pericarditis may occur.
- There is increased risk of coronary artery disease due to the chronic inflammatory state as well as of the use of steroids (accelerate atherosclerosis) and methotrexate (elevates homocysteine level). Rheumatoid arthritis appears to be an independent risk factor for multivessel coronary disease. Coronary vasculitis rarely develops.
- Secondary amyloidosis can cause cardiomyopathy and heart block.
- Valvulitis and aortitis may occur but are rarely clinically significant.
- Pulmonary hypertension may result from rheumatoid lung disease.
- Myocardial rheumatoid nodules may cause conduction defects.

Treatment:

Combination therapy with methotrexate, sulfasalazine, leflunomide, hydroxychloroquine and low dose prednisone are frequently employed. NSAIDs are no longer the mainstay of therapy. Antagonists of tumor necrosis factor (etanercept, infliximab) are effective, but they increase cardiac morbidity in patients with severe heart failure.

Seronegative Spondyloarthropathies

These conditions include ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease-associated arthritis and post infectious reactive arthritis (including Reiter syndrome).

Cardiovascular manifestations:

- Conduction disturbances particularly in patients with ankylosing spondylitis or Reiter syndrome.
- Aortic root disease with involvement of the aortic valve resulting in aortic root dilatation and aortic regurgitation.
- Less common manifestations include diastolic dysfunction, SVT, myocarditis and pericarditis.

Treatment:

- The anti-tumor necrosis factor agents (etanercept, infliximab, adalimumab) have demonstrated clinical efficacy in treating symptoms of spondylitis. Whether they will be beneficial for treating or preventing the cardiovascular manifestations of the disease is still unknown.
- The extraarticular manifestations of these diseases are treated with corticosteroids (uveitis) or surgery (aortic regurgitation, aortitis).

Systemic Lupus Erythematosus

Cardiovascular manifestations:

- Cardiovascular disease is the most common cause of death in patients with SLE. The prevalence of CV disease is comparable to that of DM.

- Pericarditis is the most common cardiac problem. Pericardial effusion, tamponade and constrictive pericarditis may occur. Pericarditis may also be a complication of lupus related renal failure.
- Atherosclerosis is the most common cause of ischemic heart disease in patients with SLE, but coronary vasculitis rarely occurs. Coronary thrombosis may develop in patients with anti-phospholipid syndrome. Coronary embolism may result from nonbacterial vegetative endocarditis.
- Myocarditis may result from immunological injury.
- Valvular involvement is common. Valvular thickening, noninfectious vegetations (Libman-Sacks endocarditis) and valvular insufficiency may occur. The vegetations are usually located on the atrial side of the mitral valve and the arterial side of the aortic valve. They may resolve or worsen overtime. The resulting fibrosis may cause valvular regurgitation and less commonly stenosis. Systemic embolism may occur.
- Pulmonary hypertension is common due to thromboembolism (related to the anti-phospholipid syndrome), intimal proliferation of pulmonary vessels, pulmonary vasospasm (associated with Raynaud disease) and rarely pulmonary arteritis.
- Infants of mothers with SLE have increased incidence of congenital complete heart block. This is due to transmission of maternal anti-Ro and anti-La antibodies in utero causing inflammation and fibrosis of the conduction system.

Treatment:

Patients with mild pericarditis are treated with NSAIDs. Corticosteroids are used for more severe disease. Large effusions are drained and if recurrent, a pericardial window may be considered.

Corticosteroids with or without adjunctive cyclophosphamide, mycophenolate or azathioprine are utilized for treatment of myocarditis, arteritis and valvulitis.

Indications for surgery are the same as for other causes of valvular dysfunction.

Antiphospholipid Antibody (APLA) syndrome

- This condition is characterized by: **(1)** the presence of anti-phospholipid antibodies (APLAs) such as lupus anticoagulant and anticardiolipin antibody in association with **(2)** unexplained recurrent venous or arterial thrombosis **or** recurrent miscarriages.
- The mere presence of APLAs does not define the clinical syndrome.
- APLA syndrome may occur in patients with SLE (20%), other autoimmune diseases and a number of infections. In absence of an underlying systemic disease, APLA syndrome is termed primary.

Pathogenesis:

Two mechanisms are proposed to explain the development of thrombosis by APLAs and lupus anticoagulants.

- Interfering with phospholipid-dependent anticoagulant pathways including activated protein C and tissue factor pathway inhibitor.
- Binding to cell surfaces and inducing cell activation.

Manifestations:

- Venous thromboembolic disease is the most common manifestations and most often leads to DVT and pulmonary embolism. Arterial thrombosis is less common and most often leads to stroke.
The presence of lupus anticoagulant is more frequently associated with venous thrombosis, whereas cardiolipin antibodies are more often associated with carotid, peripheral and coronary disease.
- Cardiovascular manifestations include: thrombotic CAD, intracardiac thrombi, nonbacterial endocarditis, heart valve abnormalities (thickening, vegetations, thrombotic masses) and pulmonary hypertension (due to chronic thromboembolism and pulmonary arterial intimal proliferation).
- Recurrent miscarriages usually in second or third trimester.

- Mild thrombocytopenia, hemolytic anemia and livido reticularis are commonly present.
- Prolongation of activated partial thromboplastin time and the dilute Russell's viper venom test (with the patient off heparin). The prolongation of the latter test is not corrected with the addition of the correct phospholipid (platelet neutralization procedure).

Treatment:

Confirmed thrombosis require anticoagulation with a target INR of 2.5-3.5. Low dose aspirin may be added.

Systemic Sclerosis (Scleroderma)

There are two forms:

- **Limited scleroderma** (CREST syndrome) consists of: **Cal**cinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly and **T**elangiectasia.
- **Generalized progressive systemic sclerosis** which is distinguished from CREST syndrome by proximal cutaneous fibrosis.

The term “**Limited**” does not indicate absence of visceral disease; it refers only to the distribution of skin lesions.

Cardiovascular manifestations:

- Raynaud phenomenon usually precedes skin "hardening" in both limited scleroderma (CREST) and generalized progressive systemic sclerosis.
- Pericarditis and pericardial effusion are common and are treated with NSAIDs. Steroids are rarely used since they may induce renal crises which compromise hypertensive episodes, renal failure, microangiopathy, thrombocytopenia and LV failure. Renal crises are 20-fold more common in the generalized disease than in CREST.

- Myocardial ischemia and infarction may occur in the generalized disease due to coronary spasm and microvascular occlusion.
- LV diastolic dysfunction frequently occurs but is rarely severe.
- Ventricular arrhythmias and conduction disturbances and sudden cardiac death may occur.
- Pulmonary hypertension occurs in both limited and generalized progressive systemic sclerosis. It may be due to pulmonary vascular disease or secondary to interstitial fibrosis. Pulmonary hypertension associated with systemic sclerosis has a worse prognosis than idiopathic PAH and untreated is associated with 2-years survival rate as low as 40%.

Treatment:

- Treatment of Raynaud vasospasm is symptomatic.
- Renal crises respond to aggressive control of blood pressure with ACEIs.
- Myositis, alveolitis and pericarditis may respond to corticosteroids. Cyclophosphamide may alter the progression of pulmonary involvement.
- Pulmonary hypertension may respond to endothelin antagonists and prostanoids. Patients commonly have multiple comorbidities that render them less than ideal for lung transplantation.
- Gastric reflux is improved by avoiding meals and liquids before reclining and administration of PPI.

Polymyositis and Dermatomyositis

Cardiovascular manifestations:

- Localized or generalized myocardial dysfunction is common, but infrequently causes clinical HF.
- Conduction defects frequently occur.
- Pulmonary hypertension can occur secondary to interstitial lung disease.

- Pericarditis, coronary arteritis and ischemic heart disease are not common but may occur when polymyositis is part of an overlap syndrome with other autoimmune diseases such as SLE.
- Dermatomyositis in older patients may be a paraneoplastic syndrome.

Treatment:

- Corticosteroids in high oral doses or pulse regimen.
- Immunosuppressive therapy with methotrexate, azathioprine, cyclosporine or tacrolimus.
- High dose intravenous immunoglobulin for refractory cases.

Vasculitis

- **Large vessel vasculitis:** Takayasu arteritis, giant cell arteritis.
- **Medium sized vasculitis:** Kawasaki disease, Polyarteritis nodosa.
- **Small vessel vasculitis:** Churg Strauss syndrome, Wegener granulomatosis.

Takayasu arteritis

This is an idiopathic large and medium vessel vasculitis of young individuals. Median age at onset is 25 years. Women are affected 10 times more than men.

Pathogenesis:

Mononuclear cell infiltrates (predominantly macrophages and T-lymphocytes) appear to have reached the vessel wall through the vasa vasorum, and subsequently migrate to the intima.

- Growth factor driven myofibroblast proliferation leads to intimal hyperplasia and fibrosis and subsequent arterial stenosis or occlusion.

- Local matrix metalloproteinase synthesis may predispose to aneurysmal formation.

Clinical picture:

- Arterial stenoses occur 3 to 4 times more often than aneurysms and result in:
 - Claudication; more common in upper than in lower extremities.
 - Pulse and blood pressure asymmetries and vascular bruit. The most common site of stenosis is the subclavian and common carotid arteries. Blood pressure in one or both arms may underestimate the pressure in the aorta.
 - Hypertension due to renal artery stenosis or less commonly suprarenal aortic stenosis.
- Aneurysms usually involving the aortic root and can lead to aortic regurgitation.
- Coronary arteritis usually involving the ostial regions infrequently occur. Patients are also at risk from secondary accelerated atherosclerosis.
- Myocarditis occurs in about 18% of patients.
- Activity of the disease is denoted by increasing extremity or visceral ischemia, malaise, myalgia, arthralgia, elevated ESR and new vascular abnormalities in sequential angiographic studies. However, many patients may not have any constitutional or new vascular symptoms and as many as 50% have normal ESR and still experience progressive disease.

Diagnostic workup:

Diagnosis is based on clinical features in conjunction with vascular imaging.

- If no contraindications are present, patients should have the entire aorta and its primary branches included in vascular imaging studies.
- FDG-PET-CT may reveal evidence of active arteritis and lead to early detection of prestenotic lesions.
- Colour duplex ultrasound is useful in assessing the subclavian and common carotid arteries.

Treatment:

- Prednisone (1 mg/kg/day) is indicated for active disease. It may allow resolution of symptoms and stabilization of arteriographic findings. However, relapses can occur with tapering of the drug.
 - Cyclophosphamide or methotrexate is used for corticosteroid resistant patients or those with relapses. Agents that block tumor necrosis factor may be dramatically beneficial.
 - Surgical correction of significant stenotic lesions, aortic root dilatation and aortic regurgitation should be considered. Histopathological examination of surgical specimens should guide the need for post operative immunosuppressive therapy.
- Angioplasty and intravascular stents have resulted in restenosis far more often than bypass which is preferred whenever feasible.

Giant Cell Arteritis

This condition consists of granulomatous inflammation of large and medium sized vessels. Affected people are older than 50 years. Women predominate. About 30-50% has concurrent polymyalgia rheumatica.

Pathogenesis:

Inflammation begins in the adventitia where the vasa vasorum are the conduit for mononuclear cells that mediate vascular injury. Activated CD 83* dendritic cells initiate the arterial wall inflammation.

Clinical picture:

- Atypical and often severe headache together with scalp and temporal artery tenderness are the most characteristic features. This may be associated with acute visual loss, polymyalgia rheumatica and pain in muscles of mastication.

- Aortitis develops in at least 15% of patients. It may involve primary branches of the aorta especially the subclavian arteries. Some patients may present with features that resemble these of Takayasu arteritis. Thoracic or abdominal aortic aneurysms and dissection may develop.
- Myocardial infarction may occur.

Diagnostic workup:

- Diagnosis can be made by the association of the clinical features and elevated ESR even without temporal artery biopsy. The diagnosis is doubtful if dramatic improvement does not occur within 24 to 72 hours of steroid therapy.
- Temporal artery biopsy would be helpful, but the yield of positive results is about 50-80% due to patchy affection of the artery. Typical histological features include intimal hypertrophy, inflammation of the intima and sub-intima, breaking up of the internal elastic lamina with giant cell, lymphocyte and plasma cell infiltration.
- Temporal artery ultrasound reveals a characteristic halo sign with concentric homogenous thickening of the arterial wall and evidence of flow disturbance and stenosis.
- FDG-PET reveals widespread arteritis with increased FDG uptake throughout the aorta, subclavian and iliac arteries in > 50% of patients.
- CT angiography and MRA adds to the capability of detecting mural inflammation, aneurysms and luminal narrowing.
- Follow up screening of thoracic aorta is recommended yearly for patients with imaging evidence of aortitis and every 2-3 years for other patients.

Treatment:

- Prednisone (1 mg/kg/day) reduce symptoms within 1-2 days and often eliminate symptoms within a week. Tapering of dose is started 2-4 weeks after resolution of clinical and laboratory abnormalities.
- Cytotoxic and other immunosuppressive agents have not proved effective.
- Low-dose aspirin should be provided to all patients to reduce cranial ischemic events (blindness and stroke).

Kawasaki Disease

This acute febrile systemic disease occurs primarily in children below 5 years of age (almost never beyond age of 8 years), and affects siblings more often than age-matched population. Asian children have the highest incidence of the disease.

Diagnosis:

Unexplained Fever lasting ≥ 5 days **plus** at least 4 of the following:

1. Bilateral conjunctival injection.
2. Mucous membrane changes: injected or fissured lips, injected pharynx or strawberry tongue.
3. Extremity abnormality, erythema of palms/soles, edema of hands/feet or generalized or peripheral desquamation (hands, feet).
4. Rash (polymorphous).
5. Cervical lymphadenopathy (usually a single node > 1.5 cm)

Cardiovascular manifestations:

- Pericardial effusion.
- Myocarditis with ventricular arrhythmias, congestive HF and mitral or aortic regurgitation.

- Coronary aneurysms usually involving the proximal segments and appearing 1 to 4 weeks after onset of fever. Thrombotic coronary occlusion may lead to MI (most common in the first year after illness) and even sudden death. Coronary angiography is not performed acutely because of the risk of precipitating MI, but can be used after 6 months to establish the degree of coronary artery involvement. About 50% of all small aneurysms will undergo angiographic regression within 1-2 years, giant aneurysms rarely regress. The vascular remodeling process in injured vessels includes fibromuscular proliferation that can lead to stenoses.
- Vasculitis may affect the aorta, coeliac, carotid, subclavian, mesenteric and pulmonary arteries.

Prognosis:

The illness is usually self-limiting within 4 to 8 weeks. Mortality is 2%.

Treatment:

- Intravenous gamma globulin: most effective if given within 10 days of the illness.
- Low dose Aspirin until the patient is afebrile. Longterm low dose aspirin is recommended for patients with echocardiogram-demonstrated aneurysms.
- Corticosteroids may be helpful in resistant cases.
- Anticoagulants for patients with multiple giant (> 8 mm) coronary aneurysms and obstructive lesions.
- Severe obstructive coronary lesions may be treated by bypass surgery, but if the disease is widespread and bypass is not feasible, cardiac transplantation should be considered.

Polyarteritis nodosa

This condition is a non-granulomatous disease of only medium-sized arteries. Peak age of onset of polyarteritis nodosa is 40-60 years.

Pathogenesis:

Vascular walls are first infiltrated by neutrophils then mononuclear cells. Necrotizing changes may follow with weakening of the vessel wall and aneurysm formation or myointimal proliferation causing stenosis and occlusion.

Clinical picture:

- Systemic symptoms occur in at least half of the patients.
- Painful skin nodules similar to erythema nodosum which may progress to skin infarction and gangrene. A deep skin biopsy specimen from an involved nodular site helps the diagnosis.
- Renal infarction and renal failure may occur. Renal biopsy should be approached with caution because of the risk of haemorrhage from microaneurysms. CTA and MRI are being increasingly used but mesenteric arteriography remains the most accurate imaging modality to identify microaneurysms.
- Segmental pulmonary infarctions.
- Cardiac manifestations include angina, MI, pericarditis, hypertension and congestive heart failure. Coronary angiography may reveal coronary artery microaneurysms, coronary arteritis or coronary spasm. CTA is an alternative imaging modality that may demonstrate coronary aneurysms.
- Neuropathy, especially mononeuritis multiplex.
- Musculoskeletal symptoms occur in more than half of the cases.

Treatment:

- Prednisone (1 mg/kg/day).
- Critically ill patients should receive pulse steroids and immunosuppressive drugs including cyclophosphamide, methotrexate or azathioprine. Infliximab is added in refractory cases.

Churg-Strauss Syndrome

This syndrome is a small vessel necrotizing vasculitis that comprises asthma, eosinophilia, pulmonary infiltrates, upper airway inflammation, and a variable frequency of renal, neurological, cutaneous and cardiac involvement. Pathologically, lesions consist of eosinophilic granulomatous infiltration and vasculitis.

Pathogenesis:

Antineutrophil cytoplasmic antibodies (ANCA) may play a role in up to 40% of patients. The immunofluorescent pattern of ANCA is usually perinuclear (P pattern) and rarely cytoplasmic (C pattern). The specific antigen targeted by p-ANCA is usually myeloperoxidase and that targeted by c-ANCA is proteinase-3.

Cardiovascular manifestations:

CV disease occurs in 15-55% of cases (usually ANCA-negative) and is the most common cause of death. It may manifest by:

- Pericarditis, myocarditis and coronary arteritis. MRI is the most sensitive mean of detecting myocardial involvement.
- Mesenteric ischemia involving the small intestine and colon.
- Congestive heart failure occurs in 15-30% of cases.

Treatment:

- Withdraw any new drugs if relevant to the production of eosinophils.
- Prednisone (1 mg/kg/day) usually produce dramatic improvement.
- Cyclophosphamide is added for critically ill patients. After 3-6 months, if remission continues, it is switched to daily azathioprine or weekly methotrexate.

- In refractory cases, intravenous immunoglobulin or TNF- α blockade may be effective.

Wegener Granulomatosis (WG)

This is a systemic necrotizing vasculitis of small vessels mainly targeting the respiratory tract and kidneys. Renal biopsy reveals a immune, focal, segmental necrotizing glomerulonephritis. The laboratory hallmark of WG is the presence of serum anti-neutrophil cytoplasmic antibodies (C-ANCA) which is associated with anti-proteinase-3 antibodies.

Cardiovascular manifestations:

- Cardiomyopathy and pericarditis.
- Coronary arteritis.
- Aortic regurgitation.
- High grade AV block.
- Complications of ischemic heart disease.

Treatment:

- Corticosteroids.
- Methotrexate and cyclophosphamide.
- Surgical valve replacement and pericardiectomy for significant valvular disease or constrictive pericarditis respectively.

Behcet disease

Cardiovascular manifestations:

- The vasculitis associated with Behcet disease predominantly affects the pulmonary arteries and veins with thrombosis being a prominent clinical feature. Most thrombi are venous and cause superficial thrombophlebitis and DVT.
- Pulmonary arterial aneurysms rarely occur and are life-threatening. Aneurysms may also occur in other arterial beds.
- Other CV complications occur in < 10% and include: pericarditis, myocarditis, intracardiac thrombosis, MI and myocardial aneurysms.

Treatment:

- Anticoagulation.
- Arterial aneurysms are targeted with cyclophosphamide and high dose prednisone to reduce inflammation before surgical intervention.
- Anti-TNF- α therapy is effective in patients with recurrent aneurysms or those who fail to respond to cyclophosphamide.

Table 35-2: Highlighted Conditions with Arteritis or Periarteritis of the Coronaries:

| Condition | Size Artery Involved | Estimated Annual Incidence | Common Clinical Characteristics | Laboratory Abnormalities | Frequency Coronary Involvement | Suggestive Coronary Angiographic Features | Suggestive Extra-Coronary Angiographic Features | Treatment |
|-----------------------------|--------------------------|----------------------------|---|---|--------------------------------|---|---|--|
| Takayasu's arteritis | Large (++) Medium (+) | 1-2 per million | Onset < 40 yrs Limb claudication Arterial bruit Asymmetric pulse/BP | ↑ ESR, CRP | 10-30% | Ostial/proximal stenosis Skip lesions | Thickening ± narrowing/occlusion of large arteries (aorta or primary branches) | Glucocorticoids Methotrexate TNF-inhibitor |
| Giant cell arteritis | Large (++) Medium (+) | 10-30 / 100,000 | Onset ≥ 50 yrs Cranial symptoms (Headache, jaw claudication, double vision, vision loss) | ↑ ESR, CRP | Rare | Tapered smooth narrowing Skip lesions | If large vessels involved: similar to Takayasu but aorta and subclavians > carotid, other | Glucocorticoids Tocilizumab |
| Polyarteritis nodosa | Medium (++) Small (+) | 4-10 per million | Skin nodules, livedo Abdominal pain Testicular pain (men) Mononeuritis multiplex | Hepatitis serologies (-) ANCA | 10-50% | Aneurysm or alternating aneurysm/narrowing (beaded pattern) | -Visceral infarcts - Aneurysms (micro or saccular) -Alternating aneurysm/narrowing (beaded pattern) | Glucocorticoids cyclophosphamide methotrexate |
| ANCA vasculitis | Medium (+) Small (++) | 1-3 / 100,000 | Recurrent sinusitis Pulmonary nodules Hemoptysis Glomerulonephritis Leukocytoclastic vasculitis | (+) p-ANCA/MPO or (+) c-ANCA/PR3 (+) Hematuria ↑ Creatinine | Rare | Non-specific | N/A | Induction: GC + (RTX or CYC) Maintenance: RTX or AZA, MTX |
| Behcet's disease | Variable | 0.2-80 / 100,000 | Oral and genital sores Ulceration GI tract | N/A | 0.5-2% | Non-specific | Venous and/or arterial thrombosis | Colchicine |

| | | | | | | | | |
|---|----------|----------------------|---|--|--------|-------------------------------------|--|--|
| | | | Ocular inflammation Venous/arterial thrombosis | | | | Pseudoaneurysm medium/large arteries | Glucocorticoid s Methotrexate TNF-inhibitor |
| IgG4-related disease | Variable | 0.3-1.0 / 100,000 | Lymphadenopathy Salivary/Lacrimal swelling Orbital pseudotumor Retroperitoneal fibrosis Autoimmune pancreatitis | ↑ IgG4 (±) | 1-3% | Aneurysm Periarteritis | Periaortitis | Glucocorticoid s Rituximab |
| Erdheim- Chester disease | Variable | Rare, unknown | Bone pain (osteosclerosis) Right atrial pseudotumor Exophthalmos Perirenal fibrosis Xanthelasma | BRAF V600E mutation on histology | 25-55% | Periarteritis (RCA > LM > other) | Periaortitis “Coated Aorta” | Interferon Cladribine BRAF-inhibitor |

Hematological disorders

Hereditary Thrombophilia disorders

The coagulation and fibrinolytic systems are two separate but linked enzyme cascades that regulate the formation and breakdown of fibrin. The blood clotting system or coagulation pathway, like the complement system, is a proteolytic cascade. Each enzyme of the pathway is present in the plasma as a zymogen (an inactive form), which, on activation, undergoes proteolytic cleavage to release the active factor from the precursor molecule. The ultimate goal of the pathway is to produce thrombin, which can then convert soluble fibrinogen into fibrin, which forms a clot. The generation of thrombin can be divided into three phases: the intrinsic and extrinsic pathways that provide alternative routes for the generation of factor X, and the final common pathway which results in thrombin formation.

Activated coagulation factors are serine proteases, and their activity is modulated by several naturally occurring plasma inhibitors. The most important inhibitors of the blood coagulation system are antithrombin, protein C, and protein S. An inherited deficiency of one of these three proteins is found in about 15% of patients who present with venous thrombosis before the age of 45.

Factor V Leiden

- Factor V Leiden (FVL) is a point mutation of factor V resulting in an elimination of the cleavage site in factor V and factor Va. This genetic defect increases the risk of thrombosis, especially in homozygous or pseudo-homozygous FVL-mutated individuals.
- FVL is an autosomal dominant genetic condition that exhibits incomplete penetrance, meaning that not every person with the mutation will develop the disease.

- The primary clinical manifestation of the factor V Leiden mutation is the risk for venous thromboembolism (VTE). However, the most common finding in individuals with factor V Leiden is a laboratory-only abnormality.
- The association between factor V Leiden and arterial thromboembolism remains controversial, and it is likely to be small if present.
- Factor V Leiden can be diagnosed by mutation analysis (genetic testing) or using a functional coagulation test for APC resistance. Testing for factor V Leiden is indicated for individuals with venous thromboembolism, especially if:
 - VTE occurs at a young age, generally speaking, less than 50 yrs of age
 - Atypical sites of clotting like visceral vein thromboses like an ovarian vein, portal vein, or renal vein thrombosis.
 - Unexplained arterial thrombosis
 - Significant family history of thrombophilia
 - In a hospitalized patient developing VTE despite being on prophylactic anticoagulation with no other definite explanation for VTE
 - Unexplained recurrent deep venous thrombosis/PE
- Testing usually is not performed in individuals with a first episode, especially if it is provoked or if it occurs in people who are older than 50 years of age.
- Management of venous thromboembolism in people with factor V Leiden mutation is the same as that of the general population. Generally, direct oral anticoagulants (DOAC) are usually used for patients with typical VTE presentations.

Protein C deficiency

- Protein C deficiency is a rare disorder, characterized by a reduction in the activity of protein C, a plasma serine protease involved in the regulation of blood coagulation. The active form of protein C, activated protein C (APC), exerts potent anticoagulant activity. A deficiency in protein C is characterized by the inability to control coagulation, resulting in the excessive formation of blood clots (thrombophilia).
- Protein C deficiency may be acquired or congenital. Congenital protein C deficiency results from mutations in the PROC gene. Protein C deficiency is an autosomal dominant condition.
- **Clinical presentation:**
 - Severe protein C deficiency resulting from congenital homozygous mutations presents in neonates as disseminated intravascular coagulation (DIC) and purpura fulminans (PF).
 - Patients with moderately severe protein C deficiency may not present until adolescence and often experience recurrent venous thrombotic events, including DVT and pulmonary emboli (PE).
 - Individuals with heterozygous protein C deficiency and mild deficiency in protein C activity can range from asymptomatic to recurrent thromboses leading to post-thrombotic syndrome.
- Protein C deficiency is treatable by replacement with protein C concentrate. Neonatal PF is controllable with protein C replacement from fresh frozen plasma (FFP) or human plasma-derived, viral inactivated protein C concentrate.

Protein S deficiency

- Protein S deficiency is a rare disorder characterized by reduced activity of protein S, a plasma serine protease with complex roles in coagulation, inflammation, and apoptosis.

- Protein S facilitates the action of activated protein C (APC) on activated factor 5 (F5a) and activated factor 8 (F8a). A deficiency in protein S characteristically demonstrates the inability to control coagulation, resulting in thrombophilia and venous thromboembolism.
- Protein S deficiency can be hereditary or acquired. The acquired deficiency is usually due to hepatic disease, nephrotic syndrome, or vitamin K deficiency. Hereditary protein S deficiency is an autosomal dominant trait caused by mutations in the PROS1 gene.
- Protein S deficiency usually manifests as VTE, and any association between protein S deficiency and arterial thrombosis appears coincidental or weak.
- Management of acute thrombosis is the same as for all acute VTE episodes, based on disease severity and hemodynamic stability. VTE management is by the administration of anticoagulation therapies such as heparin (LMWH or unfractionated), VKA, or DOAC.

Antithrombin deficiency

- Antithrombin (AT) is a physiological natural anticoagulant that inhibits procoagulant serine proteases, such as activated factor II, IX, X and XI. Hereditary AT deficiency is an autosomal dominant condition, with prevalence in the general population between 0.02% and 0.2%.
- Quantitative (type I) and qualitative (type II) defects have been described. In type I, the level of AT antigen and its activity are similarly reduced, whereas in type II variants, the AT antigen level remains normal, but the AT activity is reduced as the result of a dysfunctional protein.
- Clinical presentation may vary, depending mainly on the family history of thrombosis and type of genetic mutation. Type I AT-deficient patients usually develop thrombosis at an early age and have a tendency to recurrence. In contrast, type II AT-deficient patients have a wide clinical thrombotic presentation, ranging from mild to very severe. Of note, type IIb, or heparin-binding site mutation, carries a lower thrombotic risk.

- Patients with inherited AT deficiency who develop thrombosis require indefinite anticoagulation owing to the high thrombotic recurrence rate. Anticoagulation with VKAs is the treatment of choice. AT deficiency induces heparin resistance. Therefore, reaching a therapeutic level of anti-Xa in patients anticoagulated with heparin can be challenging, despite the administration of the appropriate heparin dose adjusted for body weight.

Dysfibrinogenemia

- Congenital fibrinogen disorders comprise two classes of plasma fibrinogen defects:
 - Type I, afibrinogenemia or hypofibrinogenemia, in which there are absent or low plasma fibrinogen antigen levels (quantitative fibrinogen deficiencies);
 - Type II, dysfibrinogenemia or hypodysfibrinogenemia, in which there are normal or reduced antigen levels associated with disproportionately low functional activity (qualitative fibrinogen deficiencies).
- Patients with congenital dysfibrinogenemia can be identified during the clinical investigation of bleeding or thrombosis, or following miscarriage. However, most individuals are asymptomatic, and are usually discovered by the prolongation of routine parameters of coagulation, such as PT and APTT
- When a congenital dysfibrinogenemia is suspected, a genetic analysis is useful to confirm the diagnosis, because it may predict the risk of clinical complications.
- If treatment for thrombosis is required, anticoagulation with LMWH rather than oral anticoagulation with vitamin K antagonists is suggested, as the INR is not a valuable measurement in cases of a prolonged baseline PT. In patients with a bleeding phenotype, fresh frozen plasma (FFP), cryoprecipitate or fibrinogen concentrates can be administered.

Hyperhomocysteinemia

- Homocysteine is an amino acid not supplied by the diet that can be converted into cysteine or recycled into methionine, an essential amino acid, with the aid of specific B vitamins. Homocysteine levels vary between men and women, with a normal range typically between 5 to 15 micromol/L.
- Hyperhomocysteinemia is when levels exceed 15 micromol/L. Homocysteine levels are generally categorized into three groups: moderate (16 to 30 micromol/L), intermediate (31 to 100 micromol/L), and severe (over 100 micromol/L).
- Elevated levels of homocysteine can increase the risk of atherosclerosis by causing endothelial layer injury, promoting inflammation, and increasing oxidative stress. However, the exact mechanism is still unknown.
- The American Heart Association explained that folic acid supplementation (0.2 to 15 mg/d) could lower homocysteine levels. In patients with homocystinuria with severe hyperhomocysteinemia, pyridoxine, folic acid, and hydroxocobalamin did reduce cardiovascular risk.

Neurological disorders

Muscular Dystrophies

These disorders constitute a group of heritable disorders with variable involvement of the cardiac include Duchenne and Becker dystrophy, myotonic dystrophy, Emery-Dreifuss dystrophy, limb girdle dystrophy and facioscapohumeral dystrophy.

Duchenne and Becker muscular dystrophy

Pathophysiology:

These are X-linked recessive disorders due to mutations of the dystrophin gene (a sarcolemmal protein in the skeletal muscle and the heart which compromises the link between the cytoskeleton and the extracellular matrix) leading to progressive muscle wasting, degeneration of cardiomyocytes and replacement fibrosis.

In Duchenne muscular dystrophy, dystrophin is nearly absent while in Becker muscular dystrophy, dystrophin is present but reduced in size and amount.

This leads to the characteristic rapidly progressive skeletal muscle disease in Duchenne and the more benign course in Becker muscular dystrophy. The heart is involved in both disorders. In Becker muscular dystrophy, cardiac involvement is variable from none or subclinical to severe cardiomyopathy independent of the severity of skeletal muscle involvement.

Prognosis:

- Duchenne dystrophy is a progressive disorder with respiratory or cardiac death by age 20-25 years.
- Becker dystrophy is less common with better prognosis and most patients survive to age 40-50 year.
- Female carriers of Duchenne and Becker muscular dystrophy are at an increased risk of dilated cardiomyopathy.

Cardiovascular manifestations:

- Thoracic deformities and a high diaphragm can alter cardiovascular examination. A reduction in the anteroposterior chest dimensions is commonly responsible for a systolic impulse displaced to the left sternal border, a grade 1-3/6 mid systolic murmur in the second left intercostals space and a loud P2. Mitral regurgitation related to posterior papillary muscle dysfunction or mitral annular dilatation may occur.
- Cardiomyopathy with predilection for involvement of the posterobasal and posterolateral left ventricle occurs in almost all patients with Duchenne dystrophy and in most patients with Becker dystrophy.
- ECG reveals tall R waves and increased R/S amplitude in VI and deep narrow Q waves in lateral precordial leads.
- Cardiac arrhythmias and sudden death may occur.

Monitoring:

- Echocardiographic screening at diagnosis or by age of 6 years and subsequently every 2 years until the age of 10 years and annually thereafter is recommended for boys with Duchenne dystrophy. Abnormalities in strain imaging, diastolic dysfunction and regional wall motion abnormalities can precede global systolic dysfunction.
- Cardiac MRI is more sensitive in detecting subclinical ventricular involvement. Regional abnormalities in the posterolateral and lateral wall occur earlier than in other areas. LV noncompaction like changes may be observed possibly resulting from compensatory mechanisms in response to the failing dystrophic myocardium.

Treatment:

- Steroids are effective in delaying skeletal muscle disease and cardiomyopathy progression.
- Drisapersen, an antisense oligonucleotide that facilitates "exon skipping" of a nonsense mutation in the dystrophin gene is clinically effective with an acceptable safety profile.

- ACEIs (perindopril), eplerenone and beta blockers prolong survival of those patients as in the usual heart failure population.
- Patients with advanced heart failure may need LV mechanical assist device and can undergo cardiac transplantation.
- ICD should be considered.

Myotonic dystrophy

An autosomal dominant disorder due to an amplified and unstable nucleotide repeat. Two genetic mutations are responsible for the disease:

- **Type I** is the most common and more severe form of the disease with greater involvement of skeletal and cardiac muscles. It is due to amplified and unstable trinucleotide **CTG** repeat on chromosome **19q 13.3**.
- **Type 2** (also called proximal myotonic dystrophy) with less severe skeletal and cardiac involvement. It is due to a large and unstable tetranucleotide repeat expansion **CCTG** on chromosome **3q 21**.

Cardiac involvement is related to the resultant dysregulation of multiple cardiac systems including sarcomeric proteins, calcium handling and connexins.

Cardiovascular manifestations:

- Arrhythmias and conduction defects due to fibrosis and fatty infiltration of the specialized conduction tissue. These are more common in type I than in type 2. Atrial arrhythmias, primarily atrial fibrillation and atrial flutter are the most common arrhythmias observed. Sudden death is common in type I due to bradyarrhythmias and VT but respiratory failure from progressive muscle dysfunction is generally the most common cause of death.
- LV systolic and diastolic dysfunction, LVH, regional wall motion abnormalities and LA dilatation.
- Mitral valve prolapse due to papillary muscle dysfunction.

- ECG commonly reveals O waves not associated with MI.
- Echocardiography may reveal delayed early diastolic relaxation of the LV (similar to the skeletal muscle myotonia).

Treatment:

- Patients presenting with arrhythmias should undergo extensive evaluation including EP study. Significant or progressive ECG abnormalities despite lack of symptoms is an indication for prophylactic pacing or more appropriately ICD implantation.
- Patients with dilated cardiomyopathy improve with ACEIs and beta blockers. The use of CRT may be appropriate in patients requiring ventricular pacing.
- Anaesthesia increases the risk of AV block and other arrhythmias. Therefore, monitoring during the perioperative period with a low threshold for prophylactic temporary pacing is recommended.

Emery-Dreifuss muscular dystrophy

This disorder is often inherited in an X-linked recessive fashion. The responsible gene is located on chromosome X and encodes for a nuclear membrane protein called emerin (which maintains cell-to-cell adhesions by its location in desmosomes and fascia adherens of the intercalated discs). Less commonly, the disease is inherited as an autosomal dominant or recessive with a candidate gene linked to chromosome 1 and encoding proteins of the nuclear membrane, lamins A and C.

Diagnosis:

The condition is characterized by a triad of: **(1)** Early contractures of the elbow, Achilles tendon and posterior cervical muscles, **(2)** Slowly progressive muscle weakness and atrophy primarily in the humeroperoneal muscles and **(3)** Cardiac involvement.

A definitive diagnosis of the disease and carrier state can be made using antiemerin antibodies.

Cardiovascular manifestations:

- Arrhythmias including AF, atrial flutter, ventricular arrhythmias and AV block are very frequent. Sudden death is common.
- Dilated cardiomyopathy may develop.

Treatment:

- Permanent pacing is recommended for conduction defects. Biventricular pacing may be needed.
- Prophylactic ICD implantation is appropriate for the majority of patients.
- Patients with LV dysfunction may benefit from appropriate pharmacological therapy.
- Heart transplantation may be needed.

Limb-girdle muscular dystrophy

- It is a heterogeneous group of disorders with autosomal recessive or dominant inheritance caused by mutation of lamin A1C, dystrophin-glycoprotein complex or dysferlin genes.
- Dilated cardiomyopathy and ECG changes similar to those of Duchenne and Becker muscle dystrophy are detected in the majority of patients.

Friedreich Ataxia

An autosomal recessive disorder with linkage to chromosome 9. The responsible gene shows an amplified and unstable trinucleotide GAA repeat which encodes for the mitochondrial protein frataxin. Decreased synthesis of frataxin leads to mitochondrial dysfunction with poor cellular responses to oxidative stress and apoptosis. The myocardium also shows deficient function of aconitase protein which is normally involved in iron homeostasis.

Cardiovascular manifestations:

- Hypertrophic cardiomyopathy characterized by concentric hypertrophy +/- LVOT obstruction.
- Dilated cardiomyopathy is less common and may represent a progressive transition from hypertrophic cardiomyopathy. Heart failure is the most common cause of death followed by respiratory dysfunction.

Treatment:

- Idebenone, a free radical scavenger may decrease the LV mass but does not improve LV systolic function.
- ICD implantation should be strongly considered.

Periodic paralysis

These are autosomal dominant disorders that result from donormanties in ion channel genes. They include hypokalemic and hyperkalemic period paralysis and Anderson-Tawil (long QT 7) syndrome.

- **Hypokalaemic periodic paralysis** is characterized by episodes of weakness associated with hypokalemia. It is due to mutation of the $\alpha 1$ subunit of the dihydropyridine-sensitive calcium channel (CACNAIS) or the α subunit of the sodium channel (**SCN4A**).
- **Hyperkaloemic periodic paralysis** also manifests with episodic weakness but with worsening symptoms on potassium supplementation. It is caused by mutation of the α subunit of **SCN4A** found on chromosome 17.

- **Andersen-Tawil syndrome** is a distinct periodic paralysis (hypo-, hyper- or normokalaemic) associated with dysmorphic features, abnormal QT-U pattern and ventricular arrhythmias. It is due to mutation of the **KCNJ2** gene that results in loss of function of the inward rectifier potassium protein Kir 2-1 that underlie the background current I_K.

Episodic weakness is more severe and prolonged with hypokalemic than with hyperkalemic periodic paralysis. Ingestion of carbohydrates can trigger an attack in hypokalaemic but may ameliorate an attack in hyperkalaemic periodic paralyses.

Cardiovascular manifestations:

- Bidirectional ventricular tachycardia and polymorphic ventricular tachycardia.
- Prolonged QT interval may occur. It may be episodic associated with hypokalaemia or antiarrhythmic therapy.
- Torsade de pointes particularly in Andersen-Tawil syndrome.
- Syncope, cardiac arrest and sudden death have been reported, most prominently in the Andersen-Tawil syndrome.

Treatment:

- Measures to normalize serum potassium level. Weakness in the hyperkalemic disease may respond to mexiletine and that of hypokalemic disease to acetazolamide.
- Beta-blockers may improve the nonsustained VT associated with prolonged QT interval.
- Amiodarone, flecainide, imipramine and pacing decrease episodes of polymorphic ventricular tachycardia in Andersen-Tawil syndrome, but ICD implantation may be needed

Mitochondrial Encephalomyopathies

This is a group of disorders resulting from mutations in mitochondrial DNA. Since mitochondrial DNA is inherited maternally, the majority of these disorders are transmitted from mother to children.

- **Kears-Sayre syndrome** is characterized by progressive external ophthalmoplegia, pigmentary retinopathy and AV block. Dilated cardiomyopathy and pre-excitation may also occur.
- **Myoclonus, epilepsy with red ragged fibres (MERRF)** is characterized by myoclonus, seizures, ataxia, dementia and skeletal muscle weakness.
- **Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS)** is characterized by encephalopathy, extremity weakness and short stature. Hypertrophic and dilated cardiomyopathy may occur with both MERRF and MELAS. Pre-excitation may occur with MELAS.
- **Leber hereditary optic neuropathy** is characterized by painless loss of central vision. It can be associated with a short PR interval, pre-excitation syndrome and supraventricular tachycardia.
- **Barth syndrome**, an X-linked disorder characterized by hypotonia, growth retardation, cyclic neutropenia and 3-methylglutaconic aciduria in children. It is caused by mutation in exons of the nuclear gene encoding the tafazzin protein.

Treatment:

- In patients with Kearns-Sayre syndrome, pacemaker implantation is indicated when conduction disease is evident.
- ICD implantation is recommended for patients with both conduction disease and a dilated cardiomyopathy.
- In the other mitochondrial disorders, screening ECG and echocardiography are recommended to look for potential cardiac involvement.

Acute Cerebrovascular Diseases

Acute cerebrovascular disease including subarachnoid hemorrhage, other stroke syndromes and head injury can be associated with severe cardiac manifestations. These may be related to abnormal autonomic function, primarily increased sympathetic and parasympathetic output.

Cardiovascular manifestations:

- ECG abnormalities are observed in up to 70% of patients with subarachnoid hemorrhage. These include ST segment elevation and depression, T wave inversion, pathological Q waves, peaked inverted T waves and prolonged QT interval.
- Atrial and ventricular tachyarrhythmias as well as bradyarrhythmias can occur. However, serious VT rarely occurs in strokes other than subarachnoid hemorrhage.
- Myocardial damage, subendocardial hemorrhage and fibrosis can occur with acute cerebrovascular disease due to local myocardial catecholamine excess.
- Cardiac troponin I elevation and echocardiographic evidence of LV dysfunction may occur in patients with subarachnoid hemorrhage.
- Pulmonary edema may accompany acute neurological insults. This may have both cardiogenic component (due to systemic hypertension) and non-cardiogenic component (pulmonary capillary leak).
- ECG abnormalities reflect unfavorable intracranial factors but do not appear to portend a poor cardiovascular outcome. However, the magnitude of peak troponin elevation is predictive for adverse patient outcome.

Treatment:

- Beta blockers are effective in decreasing the myocardial damage and in controlling the tachyarrhythmias associated with subarachnoid hemorrhage and head trauma.

- Hypokalemia has to be corrected.
- Refractory ventricular arrhythmias can be controlled with stellate ganglion blockade.

Acute Ischemic Stroke

Pathophysiology:

Acute ischemic stroke manifests by sudden development of focal neurological deficit lasting > 24 hours. Reduced cerebral blood flow leads to neural and glial death in the core of the infarct. This is surrounded by an area of diminished cerebral blood flow and functional loss of neurons and glia with the potential to survive called penumbra. Ischemia triggers a complex cascade of released excitatory amino acids, Ca^{+2} influx, release of intracellular calcium and production of free radicals.

Diagnostic workup:

The first diagnostic procedure after clinical neurological examination is CT or MRI. Diffusion-weighted MRI shows ischemia immediately. Indirect signs of cerebral ischemia can be seen in CT within 2-3 hours. Diffusion- and perfusion-weighted MRI allows identification of the penumbra. CT or MR angiography or duplex ultrasonography will identify significant stenosis or occlusion of brain-supplying arteries.

Treatment:

- The patient should be admitted to a dedicated stroke unit.
- Patients with elevated BP who are eligible for treatment with intravenous tissue plasminogen activator (rtPA) should have their BP slowly lowered to < 185/110 mmHg before thrombolytic therapy is initiated and BP should be maintained at this level for at least the first 24 hours after initiating such therapy. In patients with BP > 220/120 mmHg who do not receive IV rtPA or endovascular treatment and have no comorbid conditions

requiring acute antihypertensive treatment, the BP may be lowered by 15% during the first 24 hours after onset of stroke.

- Increased blood glucose should be lowered with insulin.
- Fever should be lowered by paracetamol or cooling blankets.
- Infections are treated with antibiotics.
- Monitoring PO₂, and PCO₂, and heart rhythm is necessary.
- Prophylaxis of DVT by LMWH, unfractionated heparin, stockings and physical activity.
- Systemic thrombolysis with recombinant tissue plasminogen activator (rtPA) given intravenously in a total dose of 0.9 mg/kg (maximum 90 mg). Administration of PA must commence within 4.5 hours of stroke onset. Aspirin, heparin and warfarin should not be given during the first 24 hours post rtPA.
- Alternatively, specialized centres may perform local thrombolysis via microcatheter with urokinase or rtPA and use thrombus extraction devices or suction devices.
- In space occupying cerebral infarction, craniotomy of the posterior fossa and resection of the ischaemic brain tissue is necessary. Malignant middle cerebral artery infarction in patients < 60 years can be treated by hemicraniotomy.

Secondary Prevention:

- Antiplatelet drugs are effective in secondary prevention after transient ischemic attacks or ischemic strokes. Aspirin monotherapy in a dose of 75-150 mg/day is recommended. Clopidogrel monotherapy in a dose of 75 mg/day is given if aspirin cannot be tolerated. The combination of low dose aspirin and extended-release dipyridamole is superior to aspirin monotherapy. Patients who had a stroke while taking aspirin may be switched to a different antiplatelet drug or add a second antiplatelet drug to aspirin.

- Symptomatic patients with significant stenosis of the internal carotid artery should preferably undergo carotid endarterectomy. The benefit of surgery increases with the degree of stenosis between 70-95% and is highest in the first 2-4 weeks after the initial transient ischemic attack or minor stroke. The benefit of surgery is lower in patients with a stenosis between 50-70%, in high degree stenosis (pseudo-occlusion), in women or when surgery is performed >12 weeks after the initial event. At present, carotid stenting has a slightly higher short-term complication rate but favourable outcomes are obtained in high-risk patients. A combination of clopidogrel 75 mg and aspirin 75-100 mg is recommended after stenting for 1-3 months.
- Patients with atherosclerotic ischemic stroke or TIA should receive high intensity statin therapy to reduce the risk of stroke and other cardiovascular event.

Gullian Barre Syndrome

This is an acute inflammatory demyelinating neuropathy characterized by peripheral, cranial and autonomic nerve dysfunction.

Cardiovascular manifestations:

- Autonomic neuropathy may result in hypertension, orthostatic hypotension, resting sinus tachycardia, loss of heart rate variability, ST segment abnormalities and both bradyarrhythmias and tachyarrhythmias.
- Life-threatening arrhythmias are common in severe cases primarily those requiring assisted ventilation. Death may occur as a consequence of an arrhythmia. systole commonly occurs with tracheal suctioning.
- Non-ambulant patients are at increased risk for deep vein thrombosis and pulmonary emboli.

Treatment:

In addition to supportive care including deep vein thrombosis prophylaxis, early plasmapheresis and immunoglobulin therapy, monitoring for cardiac arrhythmias is mandatory. Temporary or permanent pacing may be needed for bradyarrhythmias.

Myasthenia Gravis

- Myocarditis including giant cell myocarditis may occur especially in those with a thymoma.
- Arrhythmias including AF, AV block, asystole, ventricular tachycardia, sudden death and heart failure may develop. Pacing may be necessary.
- The role of immunosuppressive agents and thymectomy in improving cardiac disease is unknown.

Renal disorders

Chronic kidney disease

Definition:

Chronic kidney disease is defined by an estimated glomerular filtration rate (eGFR) of $< 60 \text{ ml/min/1.73 m}^2$ or the presence of albuminuria for > 3 months.

- eGFR is calculated using the Cockcroft-Gault equation (rely on body weight) or the modification of diet in renal disease (MDRD) equation (don't rely on body weight) ⁽⁵⁴⁵⁾.
- Microalbuminuria (random urine albumin-to-creatinine ratio [ACR] of 30-300 mg/g) and albuminuria (ACR > 300 mg/g) at any level of eGFR indicate CKD. They result from endothelial dysfunction in glomerular capillaries.

Renal disease and hypertension:

- Systemic hypertension occurs in more than 80% of patients with chronic kidney disease. Patients who remain normotensive most often have tubular and interstitial disease or obstructive uropathy as the underlying disorder.
- Factors that contribute to the development of hypertension in chronic kidney disease include:
 - Diminished sodium and water excretion
 - Increased plasma renin activity
 - Anaemia
 - Arteriovenous fistula

⁽⁵⁴⁵⁾ Creatinine represents an imperfect surrogate that entails important limitations. First, creatinine reflects only GFR and not tubular injury directly. In addition, serum concentration begins to rise many hours after AKI stabilization, when very little can be done to avoid or counteract the renal worsening in a timely manner. Furthermore, creatinine levels are also influenced by a series of variables such as age, sex, ethnicity, and muscle mass.

- After renal transplantation, hypertension develops in 25-80% of patients. It may be related to:
 - Renal artery stenosis of the transplanted or native kidneys
 - Chronic rejection
 - Native kidney disease
 - Therapy with corticosteroids or cyclosporine
 - Essential hypertension before transplantation
- Most patients with chronic renal disease and hypertension require 3 or more antihypertensive agents to achieve a goal BP of < 130/80 mmHg. Agents that antagonize the renin-angiotensin-aldosterone system often in combination with diuretics are used. Dihydropyridine CCBs monotherapy should be avoided because of relative afferent arteriolar dilatation, increased intraglomerular pressure and worsen glomerular injury.
- Special diagnostic consideration should be given to the possibility of underlying bilateral renal artery stenosis in patients with poorly controlled blood pressure, abdominal bruit, peripheral arterial disease and a marked change in serum creatinine with administration of ACE inhibitors.
- Attempts to reduce sympathetic nervous system activity to the kidneys (renal artery denervation) have not improved the BP or clinical outcomes.

Renal disease and coronary artery disease:

- Accelerated atherosclerosis: Patients with chronic kidney disease have increased propensity to atherosclerosis due to a variety of reasons:
 - Dyslipidemia: In patients with nephrotic syndrome, total cholesterol and LDL are elevated but HDL is normal or low.
 - Accelerated vascular calcification due to hyperphosphatemia, hypercalcemia, and elevated parathyroid hormone level.
 - Enhanced plaque rupture due to the highly inflammatory state associated with renal dysfunction.

- Chronic hyperactivation of the sympathetic nervous system and imbalance between endothelin and nitric oxide. These factors worsen hypertension and augment intravascular wall stress.
- In patients with renal transplantation, the use of corticosteroids and immunosuppressive drugs evokes insulin resistance and hyperlipidemia.
- Defective coagulation system: Patients with chronic kidney disease have increased thrombin generation but decreased platelet aggregation. Therefore, they can have increased rate of coronary thrombotic events and increased bleeding risks at the same time.
- Abnormal myocardial oxygen supply and demand due to:
 - Volume and pressure overload increases ventricular diastolic pressure and thus can decrease coronary perfusion pressure.
 - Increased heart rate as a result of anemia, sympathetic stimulation, arteriovenous shunt and during dialysis.
- Chronic coronary artery disease: CKD modifies the clinical presentation of chronic coronary artery disease with greater prevalence of painless ischemia particularly due to increased prevalence of DM. The sensitivity of exercise testing is low perhaps because of poor exercise capacity. Coronary arteriography is often required in patients with suspected or problematic coronary artery disease to define the coronary pathology. ECG findings similar to those of myocardial ischemia (ST segment depression and T wave inversion) may be present in many patients with chronic kidney disease without significant coronary artery disease.
- Acute coronary syndrome: In making the diagnosis of AMI in patients with CKD, troponin I is the preferred biomarker on the basis of its kinetic profile in patients with renal impairment. In general, high sensitivity cTnI serves best for diagnostic evaluation of patients with CKD or ESRD experiencing acute chest discomfort. A rise and fall of cTnI or cTnT above the 99th percentile aid in the diagnosis of acute myocardial infarction in patients with CKD and ESRD. Hemodialysis patients bear considerable hemodynamic stress during dialysis sessions. There is a relationship between ST segment depression, release of cardiac biomarkers before or during dialysis and

poor long-term survival. In patients with acute coronary syndromes, renal dysfunction is an independent predictor of mortality. Agents that require dose adjustment on the bases of creatinine clearance include low molecular weight heparin, bivalirudin and glycoprotein IIb/IIIa antagonists. Whether PCI or surgery is used in the management of multivessel disease in these patients, either procedure is associated with worsened long-term survival. Patients with more severe degrees of renal impairment ($\text{eGFR} < 15 \text{ ml/min/1.73m}^2$) and those on dialysis appear to gain no improvement in survival with interventional management.

Renal disease and arrhythmias:

- Uremia, hyperkalemia, disorders of calcium-phosphate balance and autonomic dysfunction have all been linked to higher rates of atrial and ventricular arrhythmias in patients with CKD. All arrhythmias can occur including bradyarrhythmias and heart block.
- Dose adjustment is needed for many antiarrhythmic medications including digoxin, sotalol and procainamide.
- CKD and ESRD in particular may cause elevated defibrillation thresholds and failure of ICDs.

Renal disease and valvular heart disease:

- Impaired renal function has been linked to mitral annular calcification and aortic sclerosis.
- Infective endocarditis may develop in patients with dialysis access catheters. Infection with common pathogens is associated with mortality rate greater than 50% in this setting. The combination of infective endocarditis and ESRD can be very difficult to treat on account of the continued need for the dialysis access and the delay in surgical placement of permanent arteriovenous shunts or fistulas.
- Heart murmurs in patients with chronic kidney disease can represent valvular disease, functional pulmonary or aortic valvular flow or regurgitation, transmission from arteriovenous fistula to the precordium or a venous hum.
- In ESRD, tissue and mechanical valve prosthesis demonstrate similar survival. The use of tissue valves can lessen the complicating issue of chronic anticoagulation and bleeding.

Renal disease and pericardial diseases:

Various factors contribute to the development of pericardial disease in patients with chronic renal failure. These include:

- immune mechanisms
- microscopic calcification
- infection
- uremic toxins
- hemorrhagic tendency
- hyperuricemia
- volume overload
- therapy with minoxidil

Renal disease and heart failure:

- Various factors contribute to the development of congestive heart failure in patients with chronic kidney disease:
 - Volume overload due to salt and water retention, anaemia and arteriovenous access fistula.
 - Pressure overload due to systemic hypertension.
 - decreased myocardial contractility due to hypoxaemia (during haemodialysis), subendocardial Ischaemia, certain buffers used during haemodialysis (e.g. acetate), elevated parathyroid hormone levels, metabolic and electrolyte abnormalities and "uraemic toxins".
- Patients with normal LV function may experience modest decrease in LV performance during dialysis, whereas LV performance in those with baseline systolic dysfunction often improves during the procedure.
- After renal transplantation, LV systolic and diastolic volumes and ventricular mass decrease and LVEF gradually increases over 3 to 4 months. These changes are likely related to favourable alterations of LV preload and

afterload, an increase in hematocrit value and correction of various metabolic and endocrine abnormalities of renal failure.

- The anaemia that predictably develops when eGFR drops below 60 ml/min/1.73 m² is related to relative deficiency of erythropoietin alpha and increased levels of hepcidin, tumour necrosis factor alpha, interleukins and other inflammation-related proteins that reduce erythropoiesis. Anaemia is an independent predictor of mortality in patients with heart failure, with each 1 g/dl decrease in haemoglobin resulting 13% increase in all-cause mortality. Treatment of anaemia with exogenous erythropoietin reduces mortality and increases quality of life. Erythropoietin also has a positive effect on coronary endothelium resulting in increased coronary flow reserve and it enhances myocardial repair by recruiting vascular progenitor cells which can become functional myocardial cells. However, treatment with erythropoietin and supplemental iron increase platelet activity, thrombin formation, endothelin level and worsens oxidative stress. Use of darbepoetin alfa was associated with higher rates of fatal or nonfatal stroke with no differences in rates of ESRD or death. Therefore, erythropoietin may be given only to raise hemoglobin levels to a target of 11-12 g/dl and not to be used to improve the natural history of cardiovascular disease. Iron repletion with high-dose oral or intravenous iron should be considered when there is evidence of iron deficiency.
- ACE inhibitors, ARBs (if ACE inhibitors are not tolerated) beta blockers, aldosterone antagonists and loop diuretics are all acceptable therapeutic measures in patients with CKD and congestive HF. ACE inhibitors or ARBs can be used down to an eGFR of 15 ml/min/1.73 m², below this level hyperkalemia and acceleration of the course of renal disease may develop.
- Once acute heart failure is recognized clinically, 25% of patients will develop a cardiorenal syndrome (CRS) during hospitalization. Of those, one third of patients will have serum creatinine return to baseline, one third are left with a worsened eGFR and a final third have progressive cardiorenal disease resulting in death or need for renal

replacement therapy. Treatment should aim at reducing systemic congestion but avoiding overly aggressive diuresis. Ultrafiltration is kept as a last resort because of its serious side effects.

- In patients already receiving dialysis, congestive heart failure is treated with proven therapies including ACE inhibitors, ARBs, beta blockers and additional agents for blood pressure control if needed. It should be noted that ACEIs but not ARBs are dializable.

Cardiovascular complications during dialysis

- In patients undergoing hemodialysis, the prevalence of significant coronary artery disease ranges from 25% in young nondiabetic patients to 85% in older patients with longstanding DM.
- Cardiac death in dialysis patients younger than 45 years is 100 times greater than that of the general population.
- The patient with ESRD who has been placed on dialysis is considered the highest cardiovascular risk patient in medicine, the following cardiovascular complications may occur during dialysis:
 - Systemic hypotension due to hypovolemia, baroreceptor disturbances, autonomic dysfunction or concomitant drug therapy (e.g. anti-hypertensive agents).
 - LV diastolic dysfunction.
 - Hypoxemia due to:
 - Acetate buffers which can lead to leftward shift of the hemoglobin-oxygen dissociation curve and disturb ventilation-perfusion of the lungs through its vasodilatory effect.
 - Activation of complement along cupraphane exchange membranes with consequent sequestration of leucocytes within the pulmonary vessels.
 - Electrolyte and other metabolic abnormalities.
 - Complications of the arteriovenous fistula including local ischemia and infarction of tissues distal to the fistula and RV volume overload and failure.

- Other complications include: air embolism, hemolysis, systemic toxicity with excess aluminum, calcium, polyvinyl chloride (leached from dialysis membrane and tubing) and reactions in patients using polyacrylonitrile exchange membranes while receiving ACE inhibitors.

Cardiac surgery and acute kidney injury

- Acute kidney injury (AKI) occurs in approximately 15% of patients after some cardiac surgical procedures. Off-pump surgery does not seem to lower the rate of such AKI. Rates of AKI are higher when coronary arteriography is done within a few days before surgery.
- Cardiac surgery exposes patients to many factors that cause renal tubular injury. These include endogenous/exogenous toxins (free heme, catalytic iron), metabolic factors, ischaemia and reperfusion, neurohormonal activation, inflammation and oxidative stress.
- At this time, there is no accepted forms of prophylaxis or treatment of AKI associated with cardiac surgery.

Cardiorenal syndrome (CRS)

Definition:

CRS is a pathophysiologic disorder of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

Types:

- **Type 1 CRS** (most common type) is characterized by the acute worsening of cardiac function leading to AKI. This type occurs in about 25% of hospitalized cases with ADHF. AKI can be considered an independent mortality risk factor in ADHF patients.

- **Type 2 CRS** is characterized by chronic pathological changes in cardiac function leading to kidney injury or dysfunction. Chronic kidney disease has been observed in 45-63% of chronic heart failure patients. Of note, the initial decline of GFR regularly observed after initiation of heart failure medications (ACEi, ARB, ARNI, SGLT2i) results from the reduction in glomerular pressure, but the decline in GFR either slows or remains unchanged from natural course.
- **Type 3 CRS** is characterized by acute worsening of kidney function leading to heart disease. A wide spectrum of cardiac dysfunction includes cases with acute decompensated heart failure, acute coronary syndrome, and arrhythmias.
- **Type 4 CRS** is characterized by cardiovascular involvement in patients affected by CKD at any stage. It is well established that renal dysfunction is an independent risk factor for cardiovascular disease with a higher mortality risk for MI and sudden death in CKD.
- **Type 5 CRS** takes place when cardiac and renal injury occur at the same time as it occurs in sepsis and in systemic inflammatory response syndrome (SIRS). Type 5 CRS is a recently defined clinical syndrome; thus, solid epidemiological data are not available.

Pathophysiology:

Various mechanisms playing a role in the onset of CRS have been identified:

- Increased central venous pressure and increased intra-abdominal pressure may be involved in the development of CRS in patients with cardiac impairment, as it leads to renal venous congestion and a decrease in filtration pressure.
- Decreased cardiac output activates neurohormonal pathways to increase tissue perfusion. Excessive activation of the RAAS system, and in particular high levels of angiotensin II, has been shown to have negative effects on both the heart and the kidneys.

- The vasoconstrictive capacity of angiotensin II significantly increases the afterload of the LV, while at the same time, the continuous vasoconstriction of the coronary arteries can lead to myocardial ischemia and endothelial dysfunction, especially after myocardial infarction. Angiotensin II also induces LVH and remodeling. It can impair the balance of coagulation and fibrinolysis and, in combination with the activation of the sympathetic nervous system, is a pro-inflammatory factor and activator of oxidative stress.
- Angiotensin II-induced renal injury is hypothesized to be caused by increased intrarenal vasoconstriction, leading to decreased perfusion of the renal tissue and is associated with ischemic lesions. Its action as a pro-inflammatory agent and activator of oxidative stress and its effect on renal fibroblasts are also implicated.
- Activation of the SNS leads to an increase in catecholamines in the peripheral blood, resulting in an increase in blood pressure and heart rate, which leads to increased cardiac workload and, ultimately, a decrease in cardiac output, peripheral perfusion, and further deterioration of cardiac function.
- Further mechanisms and molecular pathways, such as inflammation, oxidative stress, and imbalance of regulation mechanisms, such as ADH, have been suggested for the pathophysiology of CRS type 5.

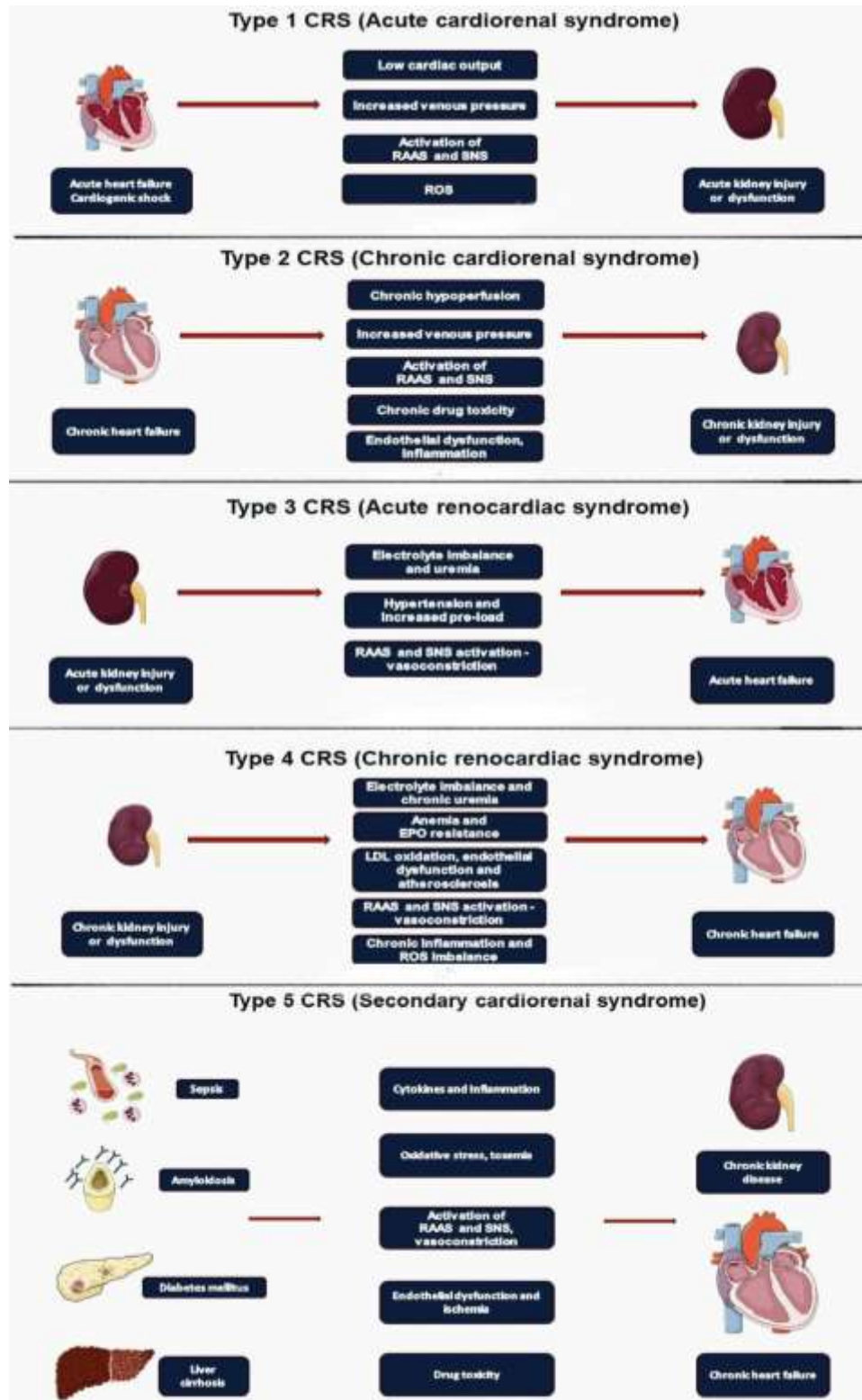


Figure 35-2: Pathogenic pathways involved in the five CRS types. Source: Mitsas AC, Elzawawi M, Mavrogeni S, et al. Heart Failure and Cardiorenal Syndrome: A Narrative Review on Pathophysiology, Diagnostic and Therapeutic Regimens—From a Cardiologist's View. Journal of Clinical Medicine. 2022 Nov 28;11(23):7041.

Diagnosis:

Establishing the diagnosis of CRS requires various tools, including non-invasive imaging modalities, adjuvant volume measurement techniques, invasive hemodynamic monitoring, and biomarkers.

- **Traditional Diagnostic Methods:**

- GFR remains the gold standard for assessing renal function. However, measuring true, real-time GFR remains difficult in the setting of ADHF or CHF because formulas estimating GFR have been validated when creatinine is in a steady state.
- A diagnosis of CRS type 2 should be based on a clinical picture of either CHF with preserved or reduced LVEF on echocardiography, joined with biochemical signs of renal dysfunction, the onset or progression of which is reasonably secondary to congestive heart failure. Further laboratory findings that are useful for a better diagnostic definition of renal damage are represented by the coexistence of albuminuria or anemia, or both.

- **Renal Biomarkers:** Biomarkers in the context of CRS can be divided into; biomarkers of renal tubular injury, and markers of glomerular filtration and integrity. Albuminuria and cystatin C are the biomarkers of glomerular filtration and integrity in CRS. Albuminuria also has an adverse prognostic value for cardiovascular death, all-cause death, and heart failure re-admissions. Urine Cystatin C is a marker of proximal tubule injury/dysfunction since it is fully metabolized in the proximal tubule. On the other hand, serum CysC levels reflect glomerular filtration.

- **Cardiac Biomarkers:** NT-proBNP is a widely used cardiac biomarker for the diagnosis and prognostic stratification of heart failure. ST2 is another protein that offers additional value to natriuretic peptide levels in predicting HF-related hospitalizations and deaths. Notably, ST2 levels are not affected by renal function. Troponins also have prognostic implications when elevated in AHF, even in the absence of underlying coronary artery disease. Elevated troponin levels are also associated with declining GFR and higher mortality.

- **Imaging of the Heart and the Kidneys:**

- Trans-thoracic echocardiography and renal ultrasound are the imaging methods of choice.
- Cardiac CT may be useful for the evaluation of coronary artery calcification (CAC). CAC is an independent predictor of CV morbidity and mortality in CKD patients.
- Cardiac MRI is a gold standard approach for the accurate assessment of biventricular function, ventricular geometry and mass, valvular pathologies, pericardial effusion, and of myocardial structure, including the localization and quantification of myocardial scars and inflammation. Of note, contrast-enhanced MRI is limited in CRS patients since severely impaired renal function ($\text{GFR} < 30 \text{ mL/min/1.73 m}^2$) is associated with nephrogenic systemic fibrosis when using gadolinium.
- Functional MRI of the kidneys has gained interest recently, especially for the detection of early changes in AKI or for the prediction of the progression of CKD.

Treatment strategies:

- **Heart Failure medications:** There is emerging evidence on the beneficial effects of heart failure treatment also on CRS outcomes. Current treatment options for both HF and CRS include:
 - Beta-blockers: have been widely used for the treatment of chronic HF, with evidence for substantial improvement of HF prognosis. However, BB therapy is not an established treatment option for patients with ADHF and in CKD patients without heart failure.
 - RAAS inhibition (ACEIs, ARBs, MRAs, ARNI) is a mainstay of HF treatment leading to improvement of prognosis. ACE-I do not slow the decline of GFR in HFrEF. ARNI preserve renal function and inhibit the progressive decline of GFR associated with HF more effectively than ACEi and ARB. RAAS inhibition may also be associated with an increased risk of hyperkalemia, particularly in patients with an $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$. For this reason, about

80% of patients with renal failure corresponding to CKD stages 3 and 4 (eGFR < 60 mL/min/1.73 m²) discontinue treatment with RAAS inhibitors or only receive submaximal doses.

- SGLT2i: causes vasoconstriction of the vas afferens and vasodilation of the vas efferens. Both together lead to a reduction in intraglomerular pressure and, thus, renal hyperfiltration. This results in the initial and reversible “dip” in the eGFR in patients subjected to SGLT2i. However, the renoprotective effects of SGLT2i have been proven in several large trials addressing CKD, both in diabetic and non-diabetic patients.
- CRT: it has been shown to improve renal function by increasing cardiac output and increasing mean arterial pressure while decreasing central venous pressure. CRT reduces SNS activity by decreasing adrenergic tone, which ultimately contributes to the improvement in renal function.
- Mechanical circulatory support may be a treatment strategy to improve renal function and reduce diuretic resistance in CRS in advanced or terminal heart failure.
- **Regulation of Volume Status:**
 - Diuretics play a key role in treating CRS since they quickly alleviate symptoms caused by fluid expansion in the patient. They positively affect hypertension, increased intra-abdominal pressure, and renal congestion. Diuretics and/or ultrafiltration are effective for the treatment of ADHF and CRS. In patients with type 1 and type 2 CRS, improvement in renal function is accompanied by improvement in cardiac function.
 - Maintaining hemodynamic stability and guaranteeing tissue perfusion are the key points to prevent type 5 CRS in the hyperacute phase of sepsis, together with fluid control and correct antibiotic treatment. Fluid therapy must be carefully controlled to avoid fluid overload.

Liver disorders

The liver receives blood from the portal vein and hepatic artery. Receiving blood from 2 vessels protects the liver: If one source fails, the liver continues to function as it is supplied by the other. Although liver mass constitutes 2.5% of total body weight, the liver receives 25% of cardiac output. On entering the liver, blood from the portal vein and hepatic artery mix and flows through sinusoids, in contact with hepatocytes, and subsequently through the hepatic veins. The hepatic veins carry blood to the inferior vena cava, which carries blood to the right side of the heart.

Hepatic Injury in Heart Failure

Mechanism:

- Ischemia reperfusion injury is characterized by cellular damage caused by hypoperfusion-induced hypoxia, which is paradoxically exacerbated after restoration of oxygen delivery. Hepatic ischemia reperfusion injury in HF is characterized by early activation of Kupffer cells, late activation of polymorphonuclear cells (“neutrophilic hepatitis”), intracellular calcium overload, cytokines and chemokines, oxidative stress, mitochondrial damage, and disruption of liver microcirculation.
- Hepatic congestion. Absence of valves in hepatic veins allows the increased IVC pressure to impact the sinusoidal bed causing centrilobular congestion, sinusoidal dilation, and perivenular fibrosis.

Acute Cardiogenic Liver Injury

Mechanism:

Although acute cardiogenic liver injury (formerly, hypoxic hepatitis, ischemic hepatitis, or shock liver) was conventionally considered the result of cardiogenic shock, there is evidence that this is not the sole responsible incident. Patients having chronic congestion, may exhibit acute cardiogenic liver injury even after mild circulatory

disturbances. In chronic congestion, hepatocytes compensate for impaired blood flow by increasing oxygen extraction. However, with inadequate liver perfusion in HF, this compensatory mechanism is exhausted, leading to hepatocellular hypoxia and necrosis.

Diagnosis:

Diagnosis is based on: **1)** setting: cardiac, circulatory, or pulmonary failure; **2)** aminotransferase levels, usually > 20 times the upper limit of normal; and **3)** exclusion of other causes of liver damage. Cardiogenic liver injury often remains asymptomatic. Laboratory tests show increased ALT and LDH, usually 1 to 3 days after hemodynamic deterioration. An ALT to LDH ratio < 1.5 denotes cardiogenic acute liver injury. Frequently, patients exhibit a bleeding diathesis derived from deficiency of liver coagulation factors. An increase in bilirubin denotes hepatocellular injury or cholestasis. Renal dysfunction is often present.

Abdominal ultrasonography can be supportive in the diagnosis. Dilation of inferior vena cava and suprahepatic veins due to passive congestion is suggestive of acute cardiogenic liver injury.

Liver biopsy is helpful under conditions where the underlying cause remains unclear.

Management:

Management focuses on the underlying acute HF. Oxygen should be considered in hypoxemic patients and intravenous inotropes in persistent hypoperfusion.

Prognosis:

Although some patients survive the acute event and aminotransferases returns to normal values within 3 to 7 days, mortality remains high.

Congestive Hepatopathy

The incidence of congestive hepatopathy is 15-65% in severe HF.

Pathophysiology:

Pathophysiology includes increased hepatic venous pressure, decreased hepatic blood flow, and decreased arterial oxygen saturation. Congenital heart disease and Fontan circulation represent other populations of patients at risk to develop liver disease.

Diagnosis:

- Signs and symptoms are obscured by concomitant right HF. In end-stage biventricular HF, restrictive, constrictive or severe tricuspid regurgitation, the differential diagnosis from chronic liver disease or cirrhosis can be challenging. A pulsatile liver reflects tricuspid regurgitation, whereas loss of this pulsation progression to secondary “cardiac liver fibrosis”.
- Patients typically present with a predominance of cholestatic enzymes. Often congestive hepatic and renal dysfunctions co-exist (hepatorenal reflex).
- Characteristic conventional imaging findings include dilation of inferior vena cava and hepatic veins; loss of normal triphasic hepatic venous waveform; retrograde hepatic venous opacification during the early phase of intravenous contrast material injection; and a predominantly peripheral heterogeneous pattern of hepatic enhancement due to stagnant blood flow. Extensive fibrosis can be seen in chronic or severe cases. Hyperenhancing regenerative nodules retaining hepatobiliary contrast agents are often present. Elastography enables noninvasive measurement of liver mechanical properties through observation of shear-wave propagation. Increasing fibrosis stage is associated with increased liver stiffness, which can be exploited by ultrasonographic and CMR elastographic methods.

- Key findings in liver biopsy are atrophy or necrosis or both, most pronounced in the central third of the hepatic lobule and most prominent immediately adjacent to the central vein. Notably, this pattern of necrosis and/or atrophy significantly decreases toward the lobule periphery.

Management:

Diuretics are the mainstay of treatment. Percutaneous mechanical support in conjunction with inotropic therapy may occasionally be necessary. Surgical treatment should be considered in cases with constrictive pericarditis, tricuspid regurgitation or stenosis, and ischemic cardiomyopathy. When appropriate, implantation of a LVAD and heart transplantation.

Heart Failure in Liver Disease

Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy is present in up to 50% of patients with cirrhosis.

Definition:

It is a syndrome characterized by systolic dysfunction (blunted increase in stress cardiac output with resting LVEF < 55%), impaired diastolic relaxation (E/A ratio < 1.0, prolonged deceleration time >200 ms), prolonged isovolumetric relaxation time (> 80 ms), and electrophysiological disturbances such as prolonged QTc interval.

Pathophysiology:

Cirrhotic cardiomyopathy has been attributed to a cirrhotic proinflammatory state leading to increased cardiomyocyte apoptosis and shift in myosin heavy chain isoform from the a subtype to the weaker b isoform. Circulatory abnormalities are predominantly due to liver-derived toxic factors causing arterial dilation and

hyperdynamic circulation. With further progression of liver failure and arterial dilation, the cardiac systolic reserve is exhausted. From that point, the heart is unable to further increase the cardiac output, resulting in arterial underfilling and decreased effective circulatory volume.

Diagnosis:

This syndrome, which is initially asymptomatic, is often misdiagnosed due to nonspecific symptoms present in advanced liver cirrhosis, such as exercise intolerance, fatigue, and dyspnea.

Various modalities of cardiac imaging have been applied. Stress testing has been used to assess systolic dysfunction and echocardiography to evaluate rest systolic dysfunction with strain techniques. Echocardiography with tissue Doppler is the method most preferred to detect diastolic dysfunction.

Prognosis:

Prognosis is unfavorable, and specific therapies are lacking. Several new vasoactive peptides (copeptin, pro-adrenomedullin, pro-atrial natriuretic peptide) have been reported to be associated with portal pressure and systemic hemodynamics, whereas galectin-3 is currently used as a marker of fibrosis.

Ventriculoarterial coupling has recently emerged as a novel risk stratification tool for the outcome of cirrhotic patients after LT.

Cirrhotic cardiomyopathy complicates several treatment modalities used in cirrhosis and/or HF. Although beta-blockers are contraindicated in cirrhosis with refractory ascites (i.e., hypotension/ exaggeration of low renal perfusion), they shorten the prolonged QTC interval and reduce bacterial translocation from the gut. Moreover, a recent randomized controlled trial in cirrhotic cardiomyopathy patients reported no differences between metoprolol and placebo in cirrhosis-related and cardiac outcomes during a 6-month follow-up. ACE inhibitors or

ARBs are contraindicated because they may aggravate the systemic vasodilatory state. Likewise, terlipressin, which is used for the treatment of renal dysfunction complicating liver disease, is contraindicated, as it may further depress cardiac function. Finally, diastolic dysfunction is associated with poorer prognosis in patients treated by transjugular intrahepatic portosystemic shunt.

Heart Failure in Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD is the most frequent liver disease. It is characterized by the accumulation of liver fat, > 5% per liver weight, in the presence of < 10 g of daily alcohol consumption.

NAFLD promotes coronary atherosclerosis and confers an increased risk for cardiomyopathy, valvular calcification, arrhythmia, and some conduction defects.

Moreover, NAFLD and its severity are independently associated with increased risk of adverse outcomes in elderly patients with acute HF.

Heart Failure after Liver Transplantation

HF may occur early (< 30 days) or late (> 30 days) after LT and it is accompanied by high mortality.

Early onset HF reflects surgical cardiovascular stress, whereas late onset HF indicates coronary atherosclerosis. Patients with pre-transplantation diastolic dysfunction need close post-transplantation follow-up for timely identification of HF.

Risk factors associated with the development of HF following LT include:

- **Medical history:** Older age, Coronary artery disease, Sex (female), Hypertension, Alcohol use, Recent/remote smoker, Diabetes mellitus, Depression, MELD score, Framingham score, Chronic kidney disease, Hepatitis C, Amyloidosis, Hemochromatosis, and Nonalcoholic steatohepatitis.
- **Laboratory parameters:** BUN, Creatinine concentration, eGFR, Plasma sodium levels, High sensitivity troponin, BNP, and Albumin level.
- **Electrocardiographic parameters:** QTc > 450 ms
- **Echocardiographic parameters:** Diastolic dysfunction pre-transplantation, LVEF pre-transplantation, Hemodynamic parameters Mean arterial pressure < 65 mmHg, Mean pulmonary artery pressure > 30 mmHg, and Pulmonary capillary wedge pressure > 15 mm Hg.

Liver and Drug Metabolism

Acute liver injury, hepatic congestion, and especially cardiac cirrhosis are associated with abnormalities of hepatic drug metabolism. Abnormal hepatic drug metabolism is also related to the severity of HF and is improved after HF management. Drugs used for HF that exhibit hepatic metabolism such as beta-blockers (carvedilol, metoprolol succinate, bisoprolol, nebivolol), ACE inhibitors (trandolapril, fosinopril), and ARBs (candesartan, losartan) should be used with caution. MRAs can be used in cirrhosis with ascites, whereas ivabradine is contraindicated. The question of whether cardiac and noncardiac liver injury lead to the same pharmacokinetic abnormalities remains unanswered.

Sleep disordered breathing

Definition:

Sleep disordered breathing (SDB) is a spectrum of sleep-related breathing disorders, including:

- **Obstructive sleep apnea (OSA)** is characterized predominantly by repetitive narrowing and closure of the upper airway during sleep.
- **Central sleep apnea (CSA)** is characterized by repetitive loss of respiratory drive due to abnormalities in neuromuscular output without prominent airway collapse. CSA-Cheyne-Stokes breathing (CSB) often occurs in association with cardiac or cerebrovascular disease-particularly heart failure or atrial fibrillation, stroke, or brain stem/high cervical cord injury.

OSA and CSA can co-occur in the same individual, complicating diagnosis and treatment.

Diagnosis:

Attended in-hospital polysomnography is the gold standard test for sleep disorders, identifying apneas (near absence of airflow for ≥ 10 s) and hypopneas ($\geq 30\%$ reduction in airflow for ≥ 10 s + either PaO_2 drop $\geq 3\%$ or cortical arousal), Apnea Hypopnea Index (AHI= apnea or hypopnea events per hour of sleep), staging sleep, quantifying sleep fragmentation, and identifying other sleep-related phenomena such as arrhythmia and periodic leg movements.

- **OSA:** AHI $\geq 5/\text{h}$ + characteristic symptoms OR AHI >15 with or without symptoms.
- **CSA:** Central AHI ≥ 5 events/hr & central apnea/hypopnea $\geq 50\%$ of total (CSB has a crescendo/decrecendo breathing amplitude pattern with a cycle length >40 s)

Severity grading:

OSA disease severity is categorized using AHI/REI cutoffs: < 5 (normal), 5-15 (mild), 15-30 (moderate), and > 30 (severe), with further assessment based on the severity of overnight hypoxemia, sleep fragmentation, and daytime sleepiness. Stronger associations with CVD incidence have been observed with an AHI > 30.

Risk factors for SDB:

- **Sex:** 2- to 4-fold more prevalent in men than in women, especially after menopause. Differences due to:
 - Men having a longer pharynx and more upper airway fat deposition and anatomic narrowing than women when obese.
 - Ventilatory drive and cortical arousal also lower in women, with shorter respiratory events, more hypopneas rather than apneas, and less oxygen desaturation with respiratory events.
- **Age:** Increased prevalence with age due to reducing airway stiffness and increasing cardiac/ metabolic/neurologic comorbidity.
- **Obesity:** 4-fold increase in OSA in obese middle-aged individuals compared with normal weight individuals due to increased fat in the tongue and parapharyngeal tissues, reduced chest wall compliance and lung volumes, and increased work of breathing. **N.B:** 20% of people with OSA are not obese.
- **Craniofacial features:**
 - A narrower oropharyngeal airway increases risk of snoring and OSA.
 - Particularly relevant in people of Asian ancestry where OSA increases with only minor changes in BMI.
 - Small or recessed jaw, brachycephalic head form, high-arched and narrow palate, large tongue and excessive soft tissue in the throat promote OSA.
- **Systemic inflammation:** Plasma CRP and IL-6, elevated insulin levels, and leptin resistance associated with changes in central and peripheral ventilatory drive and fat deposition, increasing SDB risk.
- **Genetics:** First degree relative of an individual with OSA has a 2-fold risk of OSA compared with someone without an affected relative.

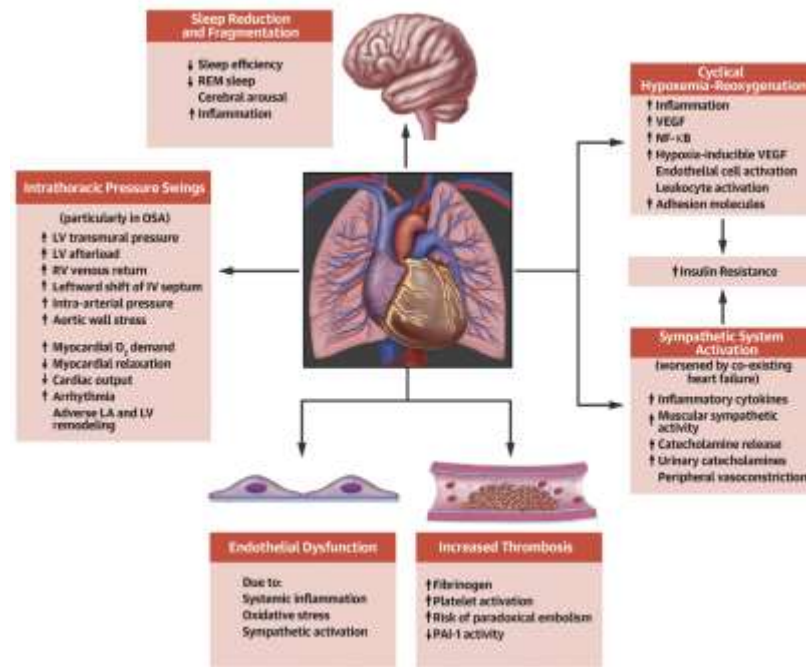


Figure 35-3: Pathophysiological Abnormalities in Sleep Disordered Breathing. Sleep disordered breathing is associated with several major pathophysiological abnormalities, including intrathoracic pressure swings (particularly in OSA), sleep reduction and fragmentation, cyclical hypoxemia and reoxygenation, sympathetic system activation, endothelial dysfunction and increased thrombosis. Nocturnal rostral fluid shifts may exacerbate both OSA and CSA. IV= interventricular; NF-κB= nuclear factor-κB; PAI-1= plasminogen activator inhibitor type-1; REM= rapid eye movement; VEGF= vascular endothelial growth factor. **Source:** Cowie MR, Linz D, Redline S, et al. Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. Journal of the American College of Cardiology. 2021 Aug

Association with CVD and outcomes:

- **Mortality.** Physician diagnosis of OSA predicted a 2.4 increase in mortality, and a higher CVD incidence, (MESA study). Predictors of mortality: AHI > 30, measures of overnight hypoxemia, periodic leg movements, numbers of awakenings, and a short sleep time.
- **Hypertension:** Up to 50% of OSA patients may have hypertension, and 30% of hypertensive patients will likely have OSA. Patients with untreated OSA followed over 4 years have a 2- to 3-fold increased risk of developing incident hypertension.
- **Coronary artery disease.** OSA is associated with increased risk of coronary events. Patients with OSA have evidence of increased arterial stiffness, early atherosclerosis, coronary artery calcification, coronary plaque instability, and increased plaque vulnerability. Acute pressor surges, hypoxemia, and adrenergic activation during apneic events may be implicated as triggers of cardiac ischemia or plaque rupture.
- **Heart Failure.** SDB is common in HF, with prevalence rates of 50-75% in HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction. In acute decompensated HF, the prevalence is between 44% and 97%. SDB is independently associated with increased mortality.
- **Pulmonary arterial hypertension.** Acute hypoxia during episodes of OSA may increase pulmonary artery pressures transiently due to hypoxic vasoconstriction. The prevalence of pulmonary hypertension in patients with OSA has been reported to be around 20% in those regardless of coexisting lung disease.
- **Arrhythmia:**
 - **Acute (transient) electrophysiological changes**
Atrium: Refractoriness ↓, Conduction velocity ↓ - Triggers ↑
Ventricle: QT dispersion ↑, Triggers ↑
 - **Chronic (progressive) cardiac remodeling**
Atrium: Atrial dilatation- Fibrosis/connexin remodeling - Conduction disturbances
Ventricle: Hypertrophy - Heart failure.

Management:

- **Lifestyle.** Individuals with OSA are advised to exercise moderately, stop smoking, avoid alcohol and sedative medication intake before sleep, and to improve sleep habits.
- **Weight loss.** Obesity is a major risk factor for OSA. Weight loss has a variable effect on the severity of OSA. Obesity may be worsened by OSA due to limitation of physical activity, reduced energy expenditure, and sleep deprivation leading to increased appetite.
- **CPAP** is established as first-line therapy in OSA patients with moderate or severe OSA due to its impact on both symptoms and quality of life. It has also been shown to improve vitality and quality of life in mild OSA. CPAP has not been proven to improve cardio-vascular outcomes, possibly because of potentially adverse effects in patients with heart failure (SAVE, RICCADSA and ISAACC).
- **Mandibular advancements splints (MAS)** can be used in patients with mild or moderate OSA, and work by lifting the mandible forward and stabilizing the upper airway.
- **Phrenic Nerve Stimulation for CSA.** Trans-venous unilateral phrenic nerve stimulation has been studied in patients with predominantly severe CSA of different etiologies. Central apnea events were nearly eliminated, with residual events being largely obstructive. Oxygen desaturation improved, as did daytime sleepiness and quality of life.
- **Acetazolamide.** Two small trials of acetazolamide have been reported to reduce AHI and improve oxygen saturation in HF and CSA, perhaps due to its respiratory stimulating properties or its diuretic action.
- **Management of HF:**
 - Optimal medical management of HF is likely to improve SDB. This should include the appropriate use of diuretic agents, which also may reduce the nocturnal rostral fluid shift that can exacerbate both OSA and CSA. CRT reduces CSA (but not OSA).
 - Adaptive Servo Ventilation (or perhaps other airway pressure therapies) for the treatment of predominantly CSA in HFREF cannot be recommended.

Iron Deficiency

Pathophysiology of iron deficiency in HF:

- In the human body, iron exists in the ferrous intracellular form (Fe^{2+}) and in the ferric form (Fe^{3+}), which is mainly extracellular and circulating. The most prominent role of iron is in oxygen homeostasis, including oxygen transport and storage, oxidative metabolism in skeletal and cardiac muscle, mitochondrial function and metabolism of proteins, lipids, and ribonucleic acids.
- Average iron intake is 10–20 mg/day. The iron homeostasis is exclusively regulated through iron absorption by the apical surface of enterocytes in the duodenum and the upper jejunum, because no means of iron excretion exists. Normally, only ~15% of dietary iron is absorbed.
- Systemic iron metabolism is predominantly regulated by hormone hepcidin and ferroportin, the only iron export protein known in mammals.
- Hepcidin blocks intestinal absorption of iron and diverts iron from the circulation, trapping it in enterocytes, hepatocytes, and macrophages. Decreased intestinal iron absorption together with its accumulation in the reticuloendothelial stores reduces the availability of iron to target tissues. Major stimuli decreasing hepcidin expression in the liver and its release into the circulation are depleted iron stores, hypoxia, and ineffective erythropoiesis, whereas inflammation produces the opposite effect.
- Because HF is characterized through high circulatory levels of inflammatory cytokines, it was initially postulated that, similar to chronic inflammatory states, HF patients have elevated levels of serum hepcidin. However, recent studies in chronic as well as acute HF showed that hepcidin levels are actually decreased in HF. Accordingly, initial premise that ID in HF is induced through limited circulatory iron availability due to metabolic mechanisms triggered by chronic inflammation is replaced with hypothesis that actually depleted iron stores are responsible for ID in HF.

Diagnosis:

- Ferritin is one of the most commonly used laboratory measures of iron status worldwide. There is a linear relationship between serum ferritin and ferritin expression in iron storage tissues, what enables usage of serum ferritin as surrogate marker of stored iron quantity and means that low circulating ferritin reflects depleted body iron stores. However, serum ferritin levels are subjected to increase in chronic and inflammatory diseases, such as HF and chronic kidney disease. Its way cut-off values for the diagnosis of ID in HF are arbitrarily set at a higher level (e.g. 100 mg/L).
- Transferrin saturation (TSAT), representing the per cent of transferrin that has iron bound to it, is used as a marker of the availability of circulating iron to supply metabolizing cells.
- In HF, absolute ID is typically diagnosed with cut-off ferritin values <100 mg/L and, distinguished from functional ID, diagnosed with normal serum ferritin (100–300 mg/L) and low TSAT (<20%).
- Newly, soluble transferrin receptor (sTfR) and hepcidin were proposed as novel serum markers for ID in HF. The sTfR indicates reduced intracellular iron availability for metabolic needs and is a reliable diagnostic tool for confirmation of ID anaemia. Importantly, the effect of chronic inflammation on circulating sTfR is minor, making sTfR a promising candidate for ID detection in chronic inflammatory states.
- Serum iron levels < 13 $\mu\text{mol/L}$ showed an excellent diagnostic accuracy of 91% for ID compared with bone marrow biopsy. However, as iron serum levels exhibit circadian variations, it cannot be used as reliable diagnostic tool for assessment of ID.
- Since the 1970s, the iron deficit in chronically ill patients was calculated using Ganzoni's formula [iron deficit = body weight \times 2.4 \times (15 - hemoglobin in g/dL) + 500 mg], assuming that ideal hemoglobin concentration amounts 15.0 g/dL (or 13.0 g/dL by body weight < 35 kg) and that additional 500 mg of iron is needed for replenishment of iron stores.

Treatment:

- Available evidence does not justify oral iron supplementation for ID in patients with chronic HF and due to unnecessary polypharmacy and possible side effects should be avoided (IRONOUT HF).
- Currently, there are five different formulations available in the USA and Europe, suitable for intravenous iron supplementation. All studies in patients with chronic HF have used either iron sucrose or ferric carboxymaltose. Intravenous iron proved to be safe in patients with HF and allows rapid correction of iron indices, particularly in instances in which intestinal absorption is compromised. The usually described side effects of intravenous iron therapy (such as hypotension, electrolyte imbalance, skin reactions, and musculoskeletal side effects) did not represent safety concern in published trials.

Cardiovascular diseases and Genetic disorders

These genetic disorders can be classified into:

- **Aneuploidy** is an abnormal number of chromosomes, and aneuploidies that most commonly survive to term include trisomy 21, 18, and 13 and sex chromosome aneuploidies such as Turner syndrome.
- **Abnormal Chromosomal structure:** include Williams syndrome.
- Syndromes caused by **single gene mutations:** including Alagille, Holt-Oram, Char, Ellis-van Creveld, Adams-Oliver, Kabuki, and CHARGE syndromes.

Aneuploidy

Down Syndrome

Down syndrome (trisomy 21) is the most common chromosomal abnormality caused by the presence of all or a portion of a third chromosome 21. It was first described by Dr. John Down in 1866, but its association with chromosome 21 was established almost 100 years later by Dr. Jerome Lejeune in Paris. The incidence of Down syndrome increases with maternal age, and its occurrence varies in different population (1 in 319 to 1 in 1000 live births).

Clinical features:

- **Congenital heart Defects (CHD):** Congenital cardiac defects are the most common and leading cause associated with morbidity and mortality in the patients with Down syndrome especially in the first 2 years of life. The incidence of CHD in babies born with Down syndrome is up to 50%. The most common cardiac defect associated with Down syndrome is an atrioventricular septal defect (AVSD), followed by a ventricular septal defect (VSD), which is seen in about 40% and 32% of the patients with Down syndrome; respectively. The other cardiac defects

associated with trisomy 21 are secundum atrial defect (10%), tetralogy of Fallot (6%), and isolated PDA (4%). Because of such a high prevalence of CHD in patients with Down syndrome, it has been recommended that all patients get an echocardiogram within the first few weeks of life.

- **Gastrointestinal Abnormalities:** Structural defects can occur anywhere from the mouth to anus, and it has been found that certain defects like duodenal and small bowel atresia or stenosis, annular pancreas, imperforate anus, and Hirschsprung disease occur more commonly in these patients. Since there is a strong association of celiac disease with Down syndrome being present in about 5% of these patients, it is recommended to do yearly screening of celiac disease. Once diagnosed, these patients will have to remain on a gluten-free diet for the rest of life.
- **Hematologic Disorders:** The hematological abnormalities in a newborn with Down syndrome (HANDS) constitute neutrophilia, thrombocytopenia, and polycythemia, which are seen in 80%, 66% and 34% of Down syndrome babies respectively. HANDS is usually mild and resolves within the first three weeks of life. The other disorder that is quite specific to Down syndrome is a transient myeloproliferative disorder, which is defined as detection of blast cells in younger than 3-month-old babies with Down syndrome. It is characterized by the clonal proliferation of megakaryocytes and is detected during the first week of life and is resolved by 3 months of life.
- **Neurologic Disorders:** Hypotonia is the hallmark of babies with Down syndrome and is present in almost all of them. Down syndrome is associated with reduced brain volume especially hippocampus and cerebellum. Dementia occurs more commonly in patients > 45 years of age, and about 84% are more prone to develop seizures. The seizures in these patients are related to the rapid decline in their cognitive functions.
- **Endocrinological Disorders:** Thyroid gland dysfunction is most commonly associated with Down syndrome. About half of the patients with Down syndrome have been shown to have subclinical hypothyroidism with elevated TSH and normal thyroxine levels. Abnormalities in sexual development are also noted to be significant with delayed puberty in both genders.

- **Musculoskeletal Disorders:** Children with Down syndrome are at an increased risk of reduced muscle mass because of hypotonia increased ligamentous laxity which causes retardation of gross motor skills and can result in joint dislocation.
- **Visual Abnormalities:** These include blepharitis (2-7%), keratoconus (5-8%), cataract (25% to 85%), retinal anomalies (0% to 38%), strabismus (23% to 44%), amblyopia (10% to 26%), nystagmus (5% to 30%), refractive errors (18% to 58%), glaucoma (less than 1%), iris anomalies (38% to 90%) and optic nerve anomalies (very few cases). The ocular anomalies, if left untreated, can significantly affect the lives of these patients. Therefore, all the patients with Down syndrome should have an eye exam is done during the first 6 months of life and then annually.
- **ENT Disorders:** The anatomical structure of the ear in Down syndrome patients predisposes them to hearing deficits. Hearing loss is usually conductive because of impaction of cerumen and middle ear pathologies that include chronic middle ear effusion due to the small eustachian tube, acute otitis media, and eardrum perforation.

Evaluation:

- Ultrasound between 14 and 24 weeks of gestation can be used as a tool for diagnosis based on the soft markers like increased nuchal fold thickness, small or no nasal bone and large ventricles. Amniocentesis and chorionic villus sampling had widely been used for the diagnosis, but there is a small risk of miscarriages between 0.5% to 1%.
- Rapid detection of trisomy 21 using FISH or QF-PCR.
- There are non-invasive prenatal diagnostic methods which are being studied to be used for the diagnosis of Down syndrome prenatally. These are based on the presence of fetal cells in the maternal blood and the presence of cell-free fetal DNA in the maternal serum.

- Other methods like digital PCR and next-generation sequencing (NGS) are also being developed for the diagnosis of Down syndrome.

Management:

- Newborn with suspicion of Down syndrome, should have a karyotyping done to confirm the diagnosis. The family needs to be referred for genetic testing and counseling of both the parents.
- Treatment is basically symptomatic and complete recovery is not possible.
- These patients should have their hearing and vision assessed and as they are more prone to have a cataract, therefore timely surgery is required. Thyroid function tests should be done on a yearly basis and if deranged should be managed accordingly.
- A balanced diet, regular exercise, and physical therapy are needed for the optimum growth and weight gain, although feeding problems do improve after the cardiac surgery.
- Cardiac referral should be sent for all the patients regardless of the clinical signs of congenital heart disease which if present should be corrected within the first 6 months of life to ensure optimum growth and development of the child.

Turner Syndrome

Turner syndrome (TS) is essentially caused by partial or complete monosomy of the X chromosome (karyotype 45X0). The incidence of AD in women with TS is 100 times as great as for women in general, occurring in the third and fourth decades of life.

Diagnosis: (based on clinical findings and cytogenetic analyses).

- Affected women display short stature, various congenital cardiac defects (coarctation of the aorta and Bicuspid aortic valve found in 12% and 30% of cases respectively), and metabolic and hormonal alterations leading to obesity, impaired glucose tolerance, hyperlipidemia, and ovarian failure.
- Hypertension and brachiofemoral delay due to coarctation of the aorta, usually identified in childhood.
- A generalized dilation of major vessels is observed, notably the aorta, the brachial, and carotid arteries.
- Elongation of the transverse arch and aortic dilation (typically at the root of the ascending aorta) are observed in 30% of cases.

Management:

The management of adult women with TS associates imaging (echocardiogram and thoracic MRI) with cardiovascular risk assessment.

Follow-up:

Follow-up will be related to risk categories (absence or number of standard cardiovascular risk factors): TTE every 3-5 years for low risk, thoracic MRI every 3-5 years for moderate risk, and referral to a cardiologist with 1-2-yearly thoracic MRI for high-risk patients.

Abnormal Chromosomal structure

William syndrome

Williams syndrome (WS) is a rare genetic and neurodevelopmental disorder. The disorder is due to deletion at chromosome band 7q11.23 that involves the elastin gene (ELN). WS often presents at birth when the child is discovered to have supra-vascular aortic stenosis. The child also shows distinctive facies (elfin-like features),

hypercalcemia, connective tissue abnormalities, growth abnormalities, intellectual disability, behavior deficits, and a gregarious personality.

Single gene mutations syndromes

LEOPARD Syndrome

LEOPARD syndrome is a rare genetic disorder, inherited in an autosomal dominant pattern. In some cases, the condition may also occur sporadically, without a family history, due to new mutations in the genes associated with the syndrome.

Features:

The term "LEOPARD" is an acronym for the different features that characterize the syndrome:

- **L- Lentigines:** Lentigines are a hallmark feature of Leopard syndrome. These dark spots typically appear in childhood and increase in number over time. These are dark-colored spots on the skin that resemble freckles but are larger and more persistent. They may be present on the face, neck, trunk, and other areas of the body.
- **E - ECG conduction abnormalities.**
- **O - Ocular hypertelorism:** It describes widely spaced eyes, caused by an increased distance between the inner corners of the eyes.
- **P - Pulmonary stenosis.** Other cardiac defects, such as hypertrophic cardiomyopathy and atrial septal defects, can also occur.
- **A - Abnormalities of the genitalia.**
- **R - Retardation of growth.**

- **D - Deafness:** Hearing loss, ranging from mild to severe, can occur in people with this condition.

Diagnosis:

The diagnosis of Leopard syndrome is typically based on the presence of characteristic features. Genetic testing can confirm the diagnosis by identifying mutations in the PTPN11 gene or other genes associated with the syndrome.

Treatment:

Treatment is focused on managing the symptoms and associated complications. Genetic counseling may also be recommended for affected individuals and their families.

Noonan Syndrome

(Male Turner syndrome)

Noonan syndrome is named after Dr. Jacqueline Noonan, who first described the syndrome in 1963. It is a genetic disorder, typically inherited in an autosomal dominant pattern. However, in some cases, the condition can occur sporadically due to new mutations in the genes associated with the syndrome. Noonan syndrome is caused by mutations in several different genes involved in the RAS-MAPK signaling pathway, which plays a critical role in cell growth and differentiation.

Features:

- **Physical Features:** Common facial characteristics include a triangular-shaped face, wide-set or downward-slanting eyes, low-set ears, a short-webbed neck, and a pectus deformity of the chest.

- **Cardiac Abnormalities** (80% of patients): The most common heart problems include pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial septal defects.
- **Developmental and Growth Delays:** Many individuals with Noonan syndrome experience developmental delays, particularly in speech and motor skills. Intellectual disability can vary widely, ranging from normal intelligence to mild to moderate intellectual impairment. Growth delays and short stature are common.
- **Other Features:** Additional features may include mild bleeding disorders, lymphatic abnormalities, skeletal abnormalities (such as scoliosis or chest deformities), and cryptorchidism (undescended testicles) in males.

Diagnosis:

Diagnosis of Noonan syndrome is based on clinical evaluation, identification of characteristic physical features, and genetic testing.

Management:

Management of Noonan syndrome involves a multidisciplinary approach. Treatment focuses on addressing the specific needs of each individual, which may include regular cardiac monitoring, growth hormone therapy for growth delays, early intervention and educational support for developmental delays, and addressing any associated medical issues.

Marfan syndrome

- Marfan syndrome is an **autosomal dominant**, age-related (that is, progressing with age) genetic disorder of the connective tissue with prominent manifestations in the skeletal, ocular and cardiovascular systems. It is the most frequent heritable connective tissue disorder.

- Marfan syndrome is essentially associated with mutations in the **FBN1 gene** that encodes **fibrillin-1** on chromosome 15, a major structural component of the extracellular matrix that provides support to connective tissues, particularly in arteries, the pericondrium and structures in the eye.
- Up to 25% of FBN1 pathogenetic variants are de novo (the mutation is new in the affected individual).

Diagnosis:

The diagnosis of Marfan syndrome is based on the **Ghent II criteria**. Requirement for the diagnosis of Marfan syndrome according to Ghent II criteria are:

- 4)** Aortic root dilatation **and** (ectopia lentis or FBN1 mutation or systemic score of ≥ 7 ⁽⁵⁴⁶⁾).
- 5)** Ectopia lentis with a FBN1 mutation known to cause ascending aorta dilatation.
- 6)** Family history of Marfan **and** (ectopia lentis or aortic root dilatation or systemic score of ≥ 7).

Management:

Management requires medical therapy to slow the rate of growth of aneurysms and decrease the risk of dissection. Both β -blockers and ARBs together are used to lessen hemodynamic stress on the aortic wall and potentially affect signalling pathways implicated in the pathogenesis of disease.

Surgery is indicated in patients who have aortic root disease with a maximal aortic sinus diameter ≥ 50 mm or ≥ 45 mm with additional risk factors (Family history of aortic dissection at a low diameter, progressive AR, desire for pregnancy, uncontrolled hypertension, and/or aortic size increase > 3 mm/year).

Systemic score: ⁽⁵⁴⁶⁾

- **3 points**= wrist and thumb sign.
- **2 points**= pectus carinatum deformity, hindfoot deformity, spontaneous pneumothorax, dural ectasia, protuberant acetabulae.
- **1 point**= wrist or thumb sign, pectus excavatum or chest asymmetry, plain flat foot, scoliosis or thoracolumbar kyphosis, reduced elbow extension, three or five facial features, skin striae, severe myopia, mitral valve prolapse.

Routine surveillance with imaging techniques such as TTE, CT or MRI is necessary to monitor aneurysm growth and determine when to perform prophylactic repair surgery to prevent aortic dissection.

Ehler-Danlos Syndrome

- Ehlers Danlos syndrome (EDS) is a group of hereditary connective tissue disorders that manifests clinically with skin hyperelasticity, hypermobility of joints, atrophic scarring, and fragility of blood vessels. In 2017, a new international classification of EDS was proposed with 13 different variants (including the vascular EDS and cardiac valvular EDS).
- Vascular EDS involves an **autosomal dominant** inheritance pattern and is associated with mutations in the **COL3A1** and/or **COL1A1** genes, which code for type III and type I **collagen**, respectively.

Diagnosis:

- **Major clinical criteria:** arterial rupture at a young age (Arteries can dissect without previous dilation and are thus unpredictable), uterine rupture (specifically 3rd trimester with no risk factors), the formation of a carotid-cavernous sinus fistula without trauma, and a family history confirmed via genetic testing.
- **Minor criteria:** Congenital hip dislocation and spontaneous pneumothorax.

Prognosis:

Individuals with vascular EDS have significantly shortened life spans (50% mortality rate by 48 years) due to the spontaneous rupture of visceral organs (colon, uterus) and blood vessels; it affects the entire vascular system and the heart.

Management:

Non-invasive imaging is the preferred approach for evaluating vascular alterations; surgery is only contemplated in potentially fatal complications, since the fragility of tissue, haemorrhagic tendency, and poor wound healing confer an added surgical risk. Prolonged post-operative monitoring is required.

N.B: Cardiac-valvular EDS involves an **autosomal recessive** inheritance pattern and is associated with mutations in the COL1A2 and/or NMD genes, which code for type I collagen.

- **Major criteria** include: skin hyperextensibility, atrophic scarring, easy bruisability, restricted or generalized joint hypermobility, and progressive cardiac-valvular problems.
- **Minor criteria** include: foot deformities, pectus deformity, joint dislocations, and inguinal hernias.

Loeys-Dietz syndrome (LDS)

First described in 2005, LDS is an **autosomal dominant** connective tissue disorder that arises from mutations altering the transforming growth factor β (**TGF- β**) signalling pathway.

It is combined of the triad of: **(1)** Arterial tortuosity and aneurysms throughout the arterial tree, **(2)** Ocular hypertelorism (increased distance between the eyes), and **(3)** High arches palate with bifid uvula.

Holt-Oram syndrome

Holt-Oram syndrome also referred to as the heart-hand syndrome, is an **autosomal dominant** disorder that is characterized by upper limb abnormalities in association with congenital heart lesions.

Holt-Oram syndrome should be suspected in individuals who present with a family history and/or the following malformations:

- Upper-limb malformation involve the carpal bones, thenar bones, and radial bones. Most cases are unilateral and affect the left side.
- Congenital heart malformation, most commonly ostium secundum ASD and VSD.
- Cardiac conduction disease: sinus bradycardia or first-degree AV block and can progress to complete heart block without warning.
- Family history of a relative with congenital heart defects

Ellis-Van Creveld syndrome

Ellis-van Creveld (EVC) syndrome is a genetic disorder with **autosomal recessive** transmission, which may clinically present as small stature, short limbs, fine sparse hair, hypoplastic fingernails, multiple musculofibrous frenula, conical teeth, hypoplasia of the enamel, hypodontia, and malocclusion.

Heart defects, especially abnormalities of atrial septation, have been found in about 60% of cases.

EVC syndrome is one of a group of diseases called ciliopathies, which is caused by abnormalities in the primary cilia (these are vibrating, hair-like projections on the surface of cells). Cilia dysfunction in EVC syndrome has been linked to a mutation in two adjacent genes on chromosome 4 (these genes are EVC and EVC2).

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), formerly Osler-Weber-Rendu, is an **autosomal dominant** disease primarily due to the gene mutations (**endoglin, ACVRL1, and SMAD4**) that affect the endothelial cell receptors of

the TGF- β . A mutation in these receptors prevents downstream signaling and disrupts angiogenesis. As a result, these vessels exhibit a loss of elasticity and remain chronically dilated.

The malformations typically manifest as mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs). These vascular malformations are responsible for much of the clinical bleeding associated with this disease, ranging from mild epistaxis to life-threatening intracranial bleeds.

Some patients with HHT develop pulmonary hypertension, prothrombotic state, or immune dysfunction.

The earliest clinical sign of HHT, often occurring by the second decade of life, is recurrent epistaxis.

The diagnosis of HHT has relied on Curaçao Criteria, which encompasses the classic features of the disease: **(1)** spontaneous, recurrent epistaxis, **(2)** positive family history, **(3)** cutaneous or mucosal telangiectasias, and **(4)** visceral lesions.

A definitive diagnosis is made if patients have 3 of the 4 criteria, and a possible or suspected diagnosis is made if patients meet 2 of the 4 criteria.

Of note, the criteria have a poor negative predictive value in children under the age of 16 years.

Lysosomal storage diseases

Lysosomal storage diseases (LSDs) are inborn errors of metabolism characterized by the accumulation of substrates in excess in various organs' cells due to the defective functioning of lysosomes. They cause dysfunction of those organs where they accumulate and contribute to great morbidity and mortality. Although rare individually, their prevalence is significant when viewed collectively.

Defective lysosomal enzymes are the chief cause. Other causes include defects in lysosomal enzyme activator, lysosomal membrane proteins, or non-lysosomal proteins.

- **Gaucher disease** is the most common lysosomal storage disorder in humans. It is an autosomal recessive, multisystem disease arising from a deficiency of beta-glucosidase activity, resulting in the accumulation of a glycolipid (glucocerebroside) within the lysosomes of macrophages, particularly in the bone marrow, spleen and the liver.
- **Pompe disease** (or glycogen storage disease type II or “acid maltase deficiency”), is caused by the absence or deficiency of acid alpha-glucosidase, which leads to the accumulation of glycogen in the lysosomes in numerous tissues, but clinical symptoms are primarily due to cardiac and skeletal muscles involvement. The disease is characterized by a wide variety of manifestations ranging from severe infantile-onset muscle weakness, hypotonia, and hypertrophic cardiomyopathy to a relatively mild slowly progressive skeletal muscle myopathy in adults.
- **Danon disease** (or glycogen storage disease Type IIb) is X-linked dominant lysosomal and glycogen storage disorder associated with HCM, skeletal muscle weakness, and intellectual disability.

Table 35-3: classifications of lysosomal storage diseases:

Sphingolipidosis:

A. GM2 gangliosidosis:

- Type A (Tay Sachs disease)
- Type O (Sandhoff disease)
- Type AB (GM2 activator deficiency)

- B. Niemann-Pick diseases A, B, and C (transmembrane protein defect C1, soluble non-enzymatic protein defect C2)
- C. Gaucher disease types 1, 2, and 3
- D. Fabry disease (classic and late-onset types)
- E. Metachromatic leukodystrophy
- F. Globoid leukodystrophy (Krabbe disease)
- G. GM1 gangliosidosis types 1, 2, and 3
- H. Multiple sulfatase deficiency

Oligosaccharidosis:

- Alfa mannosidosis
- Schindler disease
- Aspartylglucosaminuria
- Fucosidosis

Mucopolysaccharidosis:

- Hurler syndrome
- Scheie syndrome
- Hurler-Scheie syndrome
- Hunter syndrome
- SanFilippo syndrome A, B, C, and D
- Morquio syndrome A and B
- Maroteaux-Lamy syndrome
- Sly syndrome

Neuronal ceroid lipofuscinosis (lipofuscin, a waxy pigment):

- CLN 1 through CLN 14

Sialic acid disorders (sialic acid):

- Galactosialidosis (enzyme protection protein defect)
- Infantile sialic acid storage disease
- Salla disease (transmembrane protein defect)
- Sialuria

Mucopolipidosis (membrane transport protein defect; targeting error):

- Sialidosis I and II (Mucopolipidosis I)
- I-cell disease (Mucopolipidosis II)
- Pseudo-Hurler-Polydystrophy (Mucopolipidosis III)
- Mucopolipidosis IV

Miscellaneous:

- Lysosomal Acid lipase deficiency infantile and childhood/adult types (cholesterol esters, triglycerides)
- Pompe disease (glycogen storage disease type II)
- Danon disease (glycogen)
- Cystinosis (cystine)

Erectile dysfunction

Erectile dysfunction (ED) is a common predominantly vascular disease that shares the same risk factors as coronary artery disease and often presents 2-5 years before cardiac symptoms occur. Sexual activity is associated with a peak workload of 3-4 METs at orgasm. Therefore, if a person can manage at least 4 min on the treadmill without significant symptoms, ECG evidence of ischemia, a decrease in systolic blood pressure or malignant arrhythmias, it will be safe to advise on sexual activity.

ED as a predictor of occult coronary artery disease:

- The shared factors between ED and vascular disease include smoking, hyperlipidemia, diabetes, hypertension and sedentary lifestyle. Diabetics suffer from both endothelial and neurological ED with ED prevalence reported as high as 80% in those > 60 years of age. Early and vigorous glucose control, early use of statins and perhaps prophylactic daily administration of phosphodiesterase-5 inhibitors might be preventive.
- The penile arteries are considerably narrower (1-2 mm) than the coronary (3-4 mm), carotid (5-6 mm) and femoral (6-8 mm) arteries. Therefore, the same level of plaque burden and/or endothelial dysfunction has a greater effect on blood flow through the penile arteries than through the coronary, carotid and femoral arteries. Consequently, the clinical manifestations of penile endothelial dysfunction may become evident before those of the coronary or peripheral vascular disease.

High risk features that should defer sexual activity until cardiac assessment and treatment are initiated include:

- Unstable or refractory angina.
- Uncontrolled hypertension.
- Congestive heart failure (NYHA class III, IV).
- Recent myocardial infarction (within 2 weeks).
- High risk arrhythmias.
- Obstructive hypertrophic cardiomyopathy.

- Moderate to severe valve disease.

Treatment of ED in patients with CV disease:

- Lifestyle changes including cessation of smoking and control of obesity, hyperlipidemia, DM and physical inactivity. In patients with the metabolic syndrome, there is a threefold increase in the prevalence of hypogonadism.
- Drug therapy:
 - Phosphodiesterase type 5 inhibitors: These agents act by blocking the degradation of cGMP by phosphodiesterase type 5 (PDE-5) which increases the penile blood flow. PDE-5 inhibitors have a modest hypotensive action but no effect on heart rate.

The concomitant administration of PDE-5 inhibitors and nitrates (or nitric oxide donors as nicorandil) is thus contraindicated to avoid profound hypotension. Sublingual nitrates should be taken 12 hours after the PDE-5 inhibitors sildenafil or vardenafil; tadalafil which has a longer half-life ceases to react with nitrates only after 48 hours. In case of once-daily oral nitrate therapy, PDE-5 inhibitors should not be administered before 5 half-lives of their cessation (equates to 5 days). If a patient develops angina while taking a PDE-5 inhibitor, he should discontinue sexual activity and stand up as venous pooling will imitate nitrates.
 - Injection therapy: Direct intracavernosal injection of the prostaglandin E2 alprostadil dilates the penile arterioles and increases penile blood flow. The drug is effective within 5-15 minutes with erection usually lasting for 30 minutes but occasionally persisting for several hours.
 - Transurethral therapy: Intraurethral insertion of alprostadil pellet using a hand-held applicator just after micturition is an alternative to intracavernosal injection. The drug is administered about 15 minutes prior to sexual activity and a maximum of two doses are allowed per 24 hours. Success rate is up to 60%.
 - Testosterone: indicated for men with hypogonadism. It is not associated with increased CV risk.

- Non-drug therapy: This includes psychosexual therapy, vacuum constriction devices (produces erection by creating a pressure vacuum of up to 250 mmHg to increase penile blood flow) and surgical therapy.

Human Immunodeficiency Virus (HIV)

Cardiovascular effects of HIV:

- **Pericardial disease:**

Pericardial effusion is the most common cardiac manifestation of HIV infection, with an incidence of 11% per year in patients with CD4 count <200 not receiving antiretroviral therapy.

It is usually asymptomatic and small but is seen with lower CD4 counts, which implies a more advanced disease and a 2.2× increase in adjusted mortality despite the usually small size.

Patients with a moderate or large effusion may have a high risk of progression to tamponade. Also, a large or symptomatic effusion frequently, in over 50% of the cases, has a specific diagnosis: infectious (tuberculosis, purulent, opportunistic infection), or malignant (especially lymphoma or Kaposi sarcoma).

- **HIV cardiomyopathy:**

HIV cardiomyopathy is often related to a direct myocardial HIV infection, but is sometimes related to an autoimmune process triggered by HIV, coinfections (e.g., cytomegalovirus, Toxoplasma, Epstein–Barr virus), or selenium deficiency. It should be distinguished from a reversible, acute illness cardiomyopathy sometimes seen in hospitalized HIV patients. HIV cardiomyopathy is typically seen in patients with CD4 counts <400 and develops in ~8% of these patients over a 5-year follow-up; it may present as acute myocarditis.

Dilated cardiomyopathy is associated with a high mortality risk of >50% at 2 years that is partly related to the advanced HIV disease.

Patients with a progressive course should undergo an endomyocardial biopsy to rule out and treat opportunistic coinfections.

The effect of highly active antiretroviral therapy on stabilizing HIV cardiomyopathy is unclear. Diastolic dysfunction is common in HIV; in the absence of reduced EF, it may not affect the long-term prognosis.

- **Pulmonary hypertension:**

The prevalence of pulmonary arterial hypertension (PAH) in HIV is ~0.5%. PH may also be due to lung disease or left HF, which increases the overall prevalence of any PH in HIV, particularly mild PH, up to 30%. As opposed to myocardial and pericardial processes, PAH does not appear to correlate with CD4 count, and was described in patients with CD4 count over 900.

Pathologically, lesions are similar to idiopathic PAH (plexiform arteriopathy). PAH results from circulating cytokines or circulating HIV antigens activating endothelial cells. Antiretroviral therapy improves PAH and survival in these patients. Epoprostenol and bosentan were also effective in small studies.

- **Coronary artery disease:**

Patients with HIV have accelerated atherosclerosis and an almost doubled risk of MI, particularly HIV patients older than 50. The risk of MI is further increased by protease inhibitors, which increase triglycerides and the number of small LDL particles, and reduce HDL. Truncal fat redistribution (lipodystrophy) may occur with HIV regardless of the type of therapy and may lead to metabolic syndrome.

- **Endocarditis in HIV:** HIV by itself is not a risk factor for infective endocarditis but is an independent risk factor for infective endocarditis in IV drug abusers. Long-term indwelling central venous catheters, lower CD4 counts, and higher viral loads are risk factors. The incidence has decreased after introduction of ART. *Staphylococcus aureus* is the most common causative organism.

- **Cardiac tumors in HIV:** The most common causes of cardiac tumors in HIV patients are Kaposi sarcoma and B-cell lymphoma.

- **Other cardiovascular affections in HIV infection:**

- Vasculitis including systemic necrotizing vasculitis, hypersensitivity vasculitis and primary angiitis of the central nervous system.
- Autonomic dysfunction resulting in syncope, decreased heart rate variability, diarrhea, bladder dysfunction and impotence.

- Prolonged QT interval particularly with co-infection with hepatitis C
- Sudden cardiac death.

Complications of ART:

- Protease inhibitors are associated with lipodystrophy, hyperlipidemia, insulin resistance and increased atherosclerotic risk. Ritonavir has the most adverse effects on lipids.
- Zidivudine is associated with skeletal muscle myopathies.
- Non-nucleoside reverse transcriptase inhibitors are associated with altered mitochondrial DNA replication, but clinical cardiomyopathy has not been reported.
- IV pentamidine (used to treat pneumocystis) is associated with torsades de pointes.
- Medication interaction may lead to cardiac emergencies. Protease inhibitors inhibit metabolism by cytochrome P450 system and therefore increase blood levels of simvastatin, lovastatin, amiodarone, flecainide and propafenone.

Cardiac monitoring and recommendations:

- Echocardiography should be done every 1-2 years and as clinically indicated for patients at high risk or with clinical manifestations of CV disease.
- Treatment of atherosclerosis and most other disorders is similar to that of the non-HIV population, but considerable attention should be paid to drug-drug interaction.

Cocaine and The Heart

- **Myocardial ischemia:**

- **Causes:** Cocaine induces myocardial ischemia through several mechanisms:

- $\alpha+$ effect leads to coronary vasoconstriction.
- Severe HTN and tachycardia increase myocardial O₂ demands.
- Cocaine promotes platelet aggregation and thrombus formation through increased plasminogen activator inhibitor (PAI).
- Chronic cocaine use promotes atherosclerosis.

All of these effects are strongly promoted by concomitant cigarette or alcohol use (alcohol is synergistic with cocaine). Fifty percent of patients with cocaine-related MI have normal coronaries.

- **Presentation:**

Chest pain mainly occurs within 1 hour of cocaine use, but can occur up to several hours later (up to 36–96 hours later), because the concentration of active metabolites increases hours later and may lead to delayed vasoconstriction. Between 7 % and 20 % of patients presenting with chest pain to urban emergency units have a positive cocaine screen.

- **Diagnosis:**

Approximately 6% of patients with cocaine-associated chest pain have MI (as manifested by elevated CK or troponin), half of whom have normal coronary arteries.

The remaining patients have ischemia that is not sustained enough to lead to MI, or non-cardiac pleuritic pain. MI is difficult to diagnose by ECG, because many cocaine users have an abnormal baseline ECG with ST elevation (early repolarization, LVH). On the other hand, ST elevation can be related to spasm rather than thrombotic occlusion. Thus, ST elevation is sensitive but not very specific in cocaine users.

Cocaine use is diagnosed by a urinary screen of both cocaine and its metabolites. Cocaine half-life is 60–90 minutes, but its metabolites persist 24–72 hours. In chronic high-dose users, cocaine metabolites may be found for up to 2 weeks.

N.B: Always think of aortic dissection and rule it out at least clinically and by chest X-ray.

- **Treatment of cocaine-related MI or ischemia:**

- **Medical therapy:**

The following three treatments are **first-line**:

1. Aspirin.
2. Nitroglycerin, which reduces vasospasm and hypertension.
3. Benzodiazepines, which reduce the central sympathetic stimulatory effects of cocaine, and thus reduce tachycardia and hypertension.

The following therapies may be used selectively in patients with persistent hypertension or chest pain despite the first-line therapies:

4. Verapamil or diltiazem in the absence of HF, orally (preferably) or intravenously.
 5. Phentolamine (α -blocker) may be used as a second-line agent for persistent ischemia or hypertension.
- Avoid β -blockers acutely. β -Blockers increase vasospasm, as they lead to unopposed α activation. While combined α - and β -blockers may seem safe, labetalol was associated with an increased risk of seizure and death in animal studies, probably because it is much more a β - blocker than an α -blocker; thus, even α/β -blockers should be avoided acutely.
 - Most cocaine users continue to use cocaine after discharge, and chronic β -blocker therapy should therefore be avoided in most patients, except in case of a strong compelling reason, such as LV systolic dysfunction.
 - **Role of invasive management and thrombolysis:**

If chest pain persists despite the first four treatments listed above, and ECG shows persistent ST elevation, emergent coronary angiography ± PCI should be performed.

Thrombolytics are preferably avoided in cocaine users because of the concomitant hypertension that contraindicates their use, and because ST elevation may be a persistent spasm rather than a thrombus.

- **Role of stress testing:**

If chest pain resolves with the initial measures and cardiac enzymes are negative, the patient may be discharged at 12–24 hours (a stress test is optional rather than mandatory).

- **LV dysfunction is seen in 7% of chronic cocaine users:** LV dysfunction results from ischemia and/or catecholamine toxicity (contraction band necrosis, tachycardia-mediated cardiomyopathy).
- **Supraventricular or ventricular arrhythmias:** Arrhythmias mainly occur in patients with cocaine-induced myocardial ischemia or LV dysfunction.
- **Aortic dissection.**
- **Hypertensive crisis:** Hypertension may be treated with nitroglycerin, nitroprusside, nicardipine, or phentolamine.
- **Brugada pattern on ECG (RBBB with ST elevation in V1–V2).**
- **Endocarditis with intravenous cocaine use:** The intravenous use of cocaine is associated with a higher risk of endocarditis than the intravenous use of other drugs. Unlike the endocarditis associated with other drugs, the endocarditis of cocaine users more often involves the left-sided cardiac valves than the right-sided valves.

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Section

XII

Cardiovascular Pharmacology

TO THE POINT

Chapter 36:

Cardiovascular Pharmacology

Antiplatelet drugs

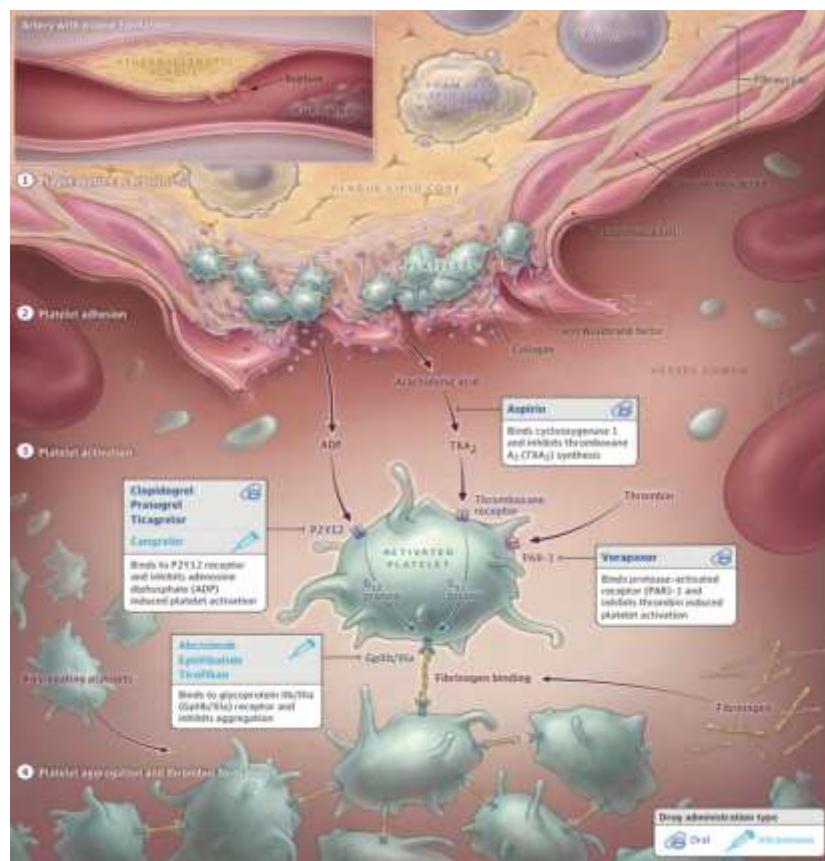


Figure 36-1: Antiplatelet Medications for ACS. **Aspirin** irreversibly inhibits platelet activation by inhibiting the cyclooxygenase-1 enzyme and blocking TxA₂ synthesis. **The P2Y₁₂ receptor inhibitors** block ADP activation of the platelet. The P2Y₁₂ receptor is required for G₁₂ protein-mediated activation of the GPIIb/IIIa receptor. This results in decreased platelet degranulation and aggregation. **Clopidogrel and prasugrel (thienopyridines)** are prodrugs that get metabolized into the same active metabolite. This active metabolite irreversibly binds to the P2Y₁₂ ADP receptor, extending the pharmacodynamic effect of these drugs to 5-7 days despite a half-life of 6 h. The prodrugs are metabolized by cytochromes (CYP), particularly CYP2C19; only 15% of clopidogrel vs. 100% of prasugrel is actively metabolized. This explains why prasugrel is a much more potent inhibitor of platelet aggregation. Clopidogrel requires a 2-step metabolism by hepatic cytochrome enzymes for biotransformation to its active form, whereas prasugrel undergoes a single-step conversion to its active metabolite. Some patients have a CYP2C19 mutation that slows clopidogrel metabolism, translating into a poor or no response to clopidogrel. Prasugrel, on the other hand, has only one metabolic pathway, and will be metabolized by cytochromes regardless of how slow the metabolism is. **Ticagrelor and cangrelor** are direct-acting reversible antagonists of the P2Y₁₂ receptor. **Abciximab, eptifibatide, and tirofiban** are intravenous direct inhibitors of the GPIIb/IIIa receptors and thereby inhibit platelet aggregation. **Vorapaxar** is an oral protease-activated receptor (PAR)-1 antagonist that inhibits thrombin-induced platelet activation by reversible binding of the PAR-1 receptor on platelets. **Source:** Kamran H, Jneid H, Kayani WT, et al. Oral antiplatelet therapy after acute coronary syndrome: a review. *Jama*. 2021 Apr 20;325(15):1545-55

Table 36-1: Summary of Oral and parenteral platelet antagonists used in cardiovascular disease:

| | Oral Antiplatelet | | | | Parenteral Antiplatelet | | | |
|--|-------------------------------|--------------|------------|-----------|-------------------------|----------------------|--------------|-----------|
| | Clopidogrel | Prasugrel | Ticagrelor | Voraxapar | Cangrelor | Tirofiban | Eptifibatide | Abciximab |
| Prodrug | Yes | Yes | No | No | No | No | No | No |
| Mech of action | P2Y12 inh/bitor | | | PAR-1 inh | P2Y12 inh | GPIIb/IIIa inh/bitor | | |
| Reversibility | Irreversible | Irreversible | Reversible | | Reversible | | | |
| Inhibition of Plt. Activation | 35-40% | 75% | 75% | | 90% | | | |
| Onset of action | 600 mg: 2 h 300 mg: 6-24 h | 30 min | 30 min | 1-2 h | 2 min | < 15 min | < 15 min | < 10 min |
| Duration of action ⁽¹⁾ | 3-10 d | 7-10 d | 3-5 d | 2-3 wk | 1-2 h | 4-8 h | 4-8 h | 24-48 h |
| Stop before surgery | 5 d | 7 d | 5 d | - | 1 h | 8 h | 8 h | > 48 h |

(1) Note that the duration of effect is related to both the pharmacokinetic half-life and the reversibility of receptor binding.

Aspirin, clopidogrel, and prasugrel have a relatively short half-life yet a very prolonged duration of action, as they irreversibly affect their target. **Ticagrelor** reversibly binds to ADP receptor but has a long half-life of ~15 h, accounting for both ticagrelor and its metabolite, which translates into a duration of action of 3-4 days.

Cangrelor reversibly binds to ADP receptor and has a very short half-life, translating into a duration of action of 1 hour.

| | | | | | | | | |
|-----------------------------------|------------|----------|-----------|---|-------------|----------------|-------------|-----------------|
| Loading dose | 300-600 mg | 60 mg | 180 mg | - | 30 µg/kg | 25 µg/kg | 180 µg/kg | 0.25 mg/kg |
| Regular dose | 75 mg OD | 10 mg OD | 90 mg BID | - | 4 µg/kg/min | 0.15 µg/kg/min | 2 µg/kg/min | 0.125 µg/kg/min |
| 50% return of plt function | | | | | | ≈4 h | ≈4 h | 12 h |

Aspirin

Mechanism of action:

Aspirin blocks the thromboxane A₂ pathway of platelet activation by irreversibly acetylating cyclooxygenase-1 enzyme. The effect of aspirin persists for the lifespan of the platelet.

Indications and Clinical evidence:

Table 36-2: Clinical trials of Aspirin:

| Trial (date) | Summary |
|---|--|
| Secondary prevention of CV disease: | |
| Antiplatelet therapy (predominantly aspirin) reduces nonfatal MI by approximately one-third, nonfatal stroke by one-third, and vascular death by one-quarter. | |
| ISIS-2 (1988) | <i>The use of aspirin 300 mg in acute MI reduced mortality by 23%.</i> |
| Primary prevention of CV disease: | |

Low-dose aspirin (75-100 mg) might be considered for the primary prevention of ASCVD among select adults aged 40-70 years who are at higher ASCVD risk but not at increased bleeding risk (AHA LoR IIb).

Low-dose aspirin should not be administered for the primary prevention of ASCVD among adults > 70 years of age or any age who are at increased risk of bleeding (AHA LoR III).

| | |
|----------------------|---|
| ASPREE (2018) | <i>ASPREE trial was a primary prevention trial that was established to investigate whether the daily use of 100 mg of aspirin would prolong the healthy life span of older adults. It showed higher all-cause mortality among healthy older adults who received daily aspirin than among those who received placebo and was attributed primarily to cancer-related death.</i> |
| ASCEND (2018) | <i>Aspirin use prevented serious vascular events in persons who had diabetes and no evident CV disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.</i> |

Aspirin Dosing:

Considering both direct and indirect comparisons of aspirin dose, the proportional reduction in vascular events was 19% with 500–1500 mg daily, 26% with 160-325 mg daily and 32% with 75-150 mg daily.

Adverse effects:

- Aspirin, even at low doses, can precipitate bronchospasm in up to 20% of asthmatic adults.
- Gastric side-effects are common and range from a feeling of nausea in the hour after the dose to major GI bleeds (Risk of bleeding from duodenal ulcers is greater than gastric ulcers).
- Risk factors for bleeding, which should be assessed, include: previous GI events, older age, and use of anticoagulants, corticosteroids, and NSAIDs. Prophylaxis with a proton pump inhibitor (PPI) should be considered in patients with multiple risk factors.
- An aspirin allergy, while not common, can occur with angioedema or overt anaphylaxis.

Contraindications:

Known allergy, active peptic ulcer, recent GI bleeding, history of recent intracranial bleeding, and bleeding disorders (e.g haemophilia ⁽¹⁾, von Willebrand disease, thrombocytopenia and severe liver disease).

Aspirin Response Variability:

The effectiveness of aspirin in clinical practice is affected by 'aspirin resistance'. This occurs relatively commonly in up to 10% of patients treated.

Much of the variability in aspirin response is believed to be due to biological variability and heritability of COX-1-independent ADP, collagen, and epinephrine responses. The COX-2 enzyme prevalent in inflammatory cells may play a role in aspirin response variability.

The most convincing data supporting genetic determination of aspirin response variability exists for the P1^A polymorphism of the ITGB3 gene encoding GPIIb. GPIIb is pivotal for platelet binding of fibrinogen, von Willebrand factor, fibronectin, and vitronectin. Carriers of P1^{A2} are more resistant to the antithrombotic effect of aspirin than carriers of P1^{A1}, and multiple studies have suggested a heightened increased risk of MI, cerebral vascular events, and venous thrombosis.

Although multiple studies and meta-analyses have documented increased risk of cardiovascular events in patients defined as in vitro nonresponders, other studies have demonstrated no difference in clinical outcomes based on in vitro aspirin responsiveness or based on genetic polymorphisms associated with in vitro resistance. As a result, routine platelet function testing is not recommended.

Drug interactions:

- *Analgesics*: avoid concomitant use with NSAIDs as this increases the risk of adverse effects.

(1) Hemophilia (A, B, or C) is not an absolute contraindication to aspirin when there are strong CV indications; however, working closely with the patient and a hematology specialist is suggested.

- *Anticoagulants*: increased risk of bleeding with warfarin and other anticoagulants. Avoid concomitant use unless there is a compelling indication for both.
- *Antidepressants*: increased risk of bleeding with SSRIs and venlafaxine.
- *Cytotoxics*: aspirin reduces the excretion of methotrexate; avoid concomitant use, or ensure close monitoring of methotrexate dose.
- Phenobarbital, phenytoin, and rifampin decrease the efficacy of aspirin through induction of the hepatic enzymes metabolizing aspirin.
- The effect of oral hypoglycemic agents and insulin may be enhanced by aspirin.

Pharmacological notes:

Aspirin is rapidly absorbed in the proximal GI tract (stomach, duodenum), achieving peak serum levels within 15-20 min and platelet inhibition within 40-60 min of oral administration. Enteric-coated preparations are less well absorbed, causing an observed delay in peak serum levels and platelet inhibition to 60 and 90 min, respectively. The antiplatelet effect occurs even before acetylsalicylic acid is detectable in peripheral blood, probably from platelet exposure in the portal circulation. The plasma concentration of aspirin decays rapidly with a circulating half-life of approximately 20 min. Despite the drug's rapid clearance, platelet inhibition persists for the platelet's life span (7 ± 2 days) due to aspirin's irreversible inactivation of COX-1. Because 10% of circulating platelets are replaced every 24 hrs, platelet activity returns toward normal (50% activity) within 5-6 days of the last aspirin dose.

P2Y₁₂ receptor antagonists

The first agent in this class, ***ticlopidine***, has been proven effective in preventing MI, stroke, TIA, and reduced mortality by 29.1% in STIMS study. However, it was associated with a risk of life-threatening blood dyscrasias, including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia. Therefore, it has been superseded in clinical

practice by the use of **clopidogrel** which has fewer serious adverse effects. **Prasugrel** was launched in 2009, and 2010 saw the introduction of **ticagrelor**.

Mechanism of action:

Adenosine diphosphate (ADP) is one of the main platelet activation factors, mediated by G-coupled receptors P2Y1 and P2Y12, and hence prevent expression of the active glycoprotein IIb/IIIa receptor.

Among the P2Y12 receptor inhibitors, there is two groups:

- **Thienopyridines** include ticlopidine, clopidogrel and prasugrel, all of which are orally administered prodrugs leading to irreversible P2Y12 receptor inhibition.
- **Non-thienopyridine derivatives** (including ticagrelor and cangrelor) do not require metabolic activation and lead to a reversible P2Y12 receptor inhibition in contrast to thienopyridines.

Clopidogrel

Clopidogrel, a thienopyridine derivative, is a platelet antagonist that is several times more potent than ticlopidine but associated with fewer adverse effects.

Indications and Clinical evidence:

| Table 36-3: Clinical trials of Clopidogrel: | |
|---|--|
| Trial (date) | Summary |
| Secondary prevention of cardiovascular events: | |
| Clopidogrel monotherapy is licensed for the secondary prevention of CV events in patients post MI or stroke, or with peripheral vascular disease. Clopidogrel should not be used for the primary prevention of CV events. | |
| CAPRIE (1997) | <i>Clopidogrel demonstrated a small advantage over aspirin in terms of protecting patients from recurrent CV events. Therefore, clopidogrel should only be employed for monotherapy in patients who are unable to tolerate aspirin first line.</i> |
| CURE (2001) | <i>In patients with NSTEMI-ACS who presented within 24 hrs after the onset of symptoms, clopidogrel (300 mg immediately, followed by 75 mg once daily) in addition to aspirin for 3 to 12 months have demonstrated a 2% reduction in major CV events.</i> |
| CHARISMA (2006) | <i>In patients with either CV disease or multiple risk factors, Clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or CV mortality.</i> |
| Efficacy of high dose clopidogrel: | |
| CURRENT-OASIS7 (2010) | <i>In patients with ACS, high-dose clopidogrel and high-dose aspirin are not superior to standard-dose clopidogrel and low-dose aspirin, respectively, in reducing CV events at 30 days. Moreover, high-dose clopidogrel results in a significant increase in major bleeding, as compared with standard-dose; high-dose aspirin results in similar major bleeding as low-dose aspirin.</i> |

Adverse effects:

- The single most troubling adverse effect is **skin rash**. Care should be taken to distinguish self-limiting radiation or contrast-induced skin rash, which occurs early (within one week of PCI), to avoid unnecessary cessation of clopidogrel. Minor rashes may be managed by use of antihistamines, but often alternative therapies such as prasugrel will be required.
- GI side-effects are reported relatively commonly, and include diarrhoea, abdominal pain, and dyspepsia.
- Bleeding and bruising are common, particularly where aspirin and clopidogrel are used in combination.
- Idiopathic thrombocytopenic purpura (ITP) and TTP have been reported with clopidogrel (rare).

Contraindications:

Hypersensitivity to clopidogrel, severe hepatic impairment, active pathological bleeding

Drug interactions:

- *Anticoagulants*: concomitant use of clopidogrel with warfarin is not routinely recommended due to the increased risk of bleeding.
- Coadministration of clopidogrel with PPI (particularly omeprazole and esomeprazole), lipophilic statins, and CCBs metabolized via CYP2C19 and CYP3A4 causes a diminished pharmacodynamics response to clopidogrel. Controversy remains, however, as to the clinical consequences of these interactions with respect to ischemic events.

Clopidogrel resistance:

Clopidogrel resistance is seen in ~30% of patients. It is defined as < 30% inhibition of ADP-induced platelet aggregation; or as an absolute platelet reactivity to ADP < 208-230 platelet reactivity units.

Clopidogrel resistance is related to impaired clopidogrel activation and is at least partly genetic, determined by mutations of the cytochrome genes (particularly CYP2C19). Other factors, such as ACS presentation, obesity, and CKD may contribute.

Poor clopidogrel response is associated with an increased risk of coronary events and stent thrombosis. However, in hyporesponsive patients undergoing PCI for stable CAD, the tailored use of prasugrel or a higher clopidogrel maintenance (150 mg) did not translate into a clinical benefit (TRIGGER-PCI). Even in ACS PCI, where poor clopidogrel response is particularly predictive of poor outcomes, tailored therapy was not superior to indiscriminate clopidogrel therapy.

Pharmacological notes:

- Clopidogrel is rapidly absorbed following oral administration with peak plasma levels of the predominant circulating metabolite occurring approximately 60 min later.
- As a prodrug, it is extensively metabolized in the liver to an active compound with a plasma elimination half-life of 7.7 ± 2.3 hrs. A 600-mg oral loading dose achieves effective platelet inhibition in 2-3 hrs.
- A 600-mg dose of clopidogrel achieves maximal inhibition of the P2Y₁₂ receptor within 2 to 4 hours.
- Repeated doses of 75 mg clopidogrel per day (without a loading dose) inhibit aggregation with steady state being reached between day 3 and day 7.

Prasugrel

Like clopidogrel, prasugrel is a thienopyridine but has a faster onset of action, acting within 30 to 60 minutes. Prasugrel is hydrolyzed by intestinal esterases to a thiolactone intermediate that is activated by a cytochrome P450-dependent step to form its active metabolite. This active metabolite binds irreversibly to the P2Y₁₂ receptor to inhibit platelet activation and aggregation. Prasugrel has less inter-patient variability in terms of antiplatelet response.

Indications and Clinical evidence:

| Table 36-4: Clinical trials of Prasugrel: | |
|---|---------|
| Trial (date) | Summary |

Secondary prevention of CV events:

Prasugrel, used in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI.

Patients with a history of stroke or TIA did worse on prasugrel than on clopidogrel, and as a result this is a contraindication to therapy. Prasugrel is more effective than clopidogrel in patients with diabetes.

| | |
|------------------------------|---|
| TRITON-TIMI-38 (2007) | <i>In patients with moderate-to-high-risk ACS with scheduled PCI, Prasugrel as compared with clopidogrel was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups.</i> |
| TRILOGY-ACS (2012) | <i>Among patients with NSTEMI-ACS, prasugrel did not significantly reduce the frequency of the primary end point, as compared with clopidogrel, and similar risks of bleeding were observed.</i> |
| ACCOAST (2013) | <i>In patients with NSTEMI who were scheduled to undergo coronary angiography within 2 to 48 hours, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications.</i> |

Adverse effects:

- Bleeding occurs commonly and is particularly problematic in the elderly (> 75 years) or patients of low body weight (< 60 kg), so a lower maintenance dose may be considered in these groups.
- Anemia, epistaxis, GI hemorrhage, hematuria.
- Rashes.

Contraindications:

Hypersensitivity, history of CVA or TIA, active bleeding disorder, severe hepatic impairment.

Cautions:

Those at increased risk of bleeding: elderly (> 75 years), low body weight < 60 kg ⁽¹⁾, renal impairment, moderate hepatic impairment, Asian patients (due to limited clinical experience), pregnancy, and lactation.

Pharmacological notes:

Prasugrel, a prodrug, undergoes rapid deesterification to an intermediate thiolactone, which is then converted to the active metabolite via a single CYP-dependent step.

Maximal plasma concentrations of active metabolite are reached within 0.5 hours after oral administration.

Inhibition of ADP binding to the platelet P2Y₁₂ receptor begins 15-30 min after administration of a 60 mg loading dose, and a maximal 60-70% platelet inhibition is achieved at 2-4 hours.

During maintenance therapy with 10 mg daily dosing, there is a steady state of 50% platelet inhibition.

After discontinuation of prasugrel, platelet aggregation returns to pretreatment levels within 7-10 days.

When compared to clopidogrel, administration of prasugrel results in earlier production and greater concentration of the equipotent active metabolites. Subsequently, prasugrel produces a more rapid onset and more consistent and greater level of platelet inhibition than clopidogrel.

Ticagrelor

Unlike clopidogrel and prasugrel, ticagrelor is not a thienopyridine. Ticagrelor is a direct-acting reversible antagonist of the P2Y₁₂ receptor. It is associated with faster onset (peak activity within 30 min) and shorter half-life (8-12 hrs) than clopidogrel.

(1) Prasugrel is generally not recommended for patients with ACS who are > 75 years or weigh < 60 kg because no net clinical benefit was seen for these groups. A 5-mg daily maintenance dose can be considered for patients weighing less than 60 kg if prasugrel is used.

Indications & clinical evidence:

| Table 36-5: Clinical trials of Ticagrelor: | |
|---|--|
| Trial (date) | Summary |
| Secondary prevention of cardiovascular events: | |
| PLATO (2009) | <i>In patients admitted to with ACS, ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, MI, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.</i> |
| PEGASUS-TIMI 54 (2015) | <i>In patients who had had MI 1-3 years earlier, Ticagrelor in addition to low-dose aspirin significantly reduced the risk of CV death, MI, or stroke and increased the risk of major bleeding.</i> |
| EUCLID (2017) | <i>In patients with symptomatic peripheral artery disease, no significant differences were found between ticagrelor and clopidogrel for reduction of cardiovascular or acute limb events.</i> |

Adverse effects:

- Ticagrelor-induced non-exertional dyspnea occurs in 10-20% of patients and is thought to be related to ticagrelor-induced elevation in adenosine levels. In many patients, ticagrelor-related dyspnea improves within the first week of treatment and only 4% of patients discontinue ticagrelor for this adverse effect.

Reversal of Ticagrelor

Bentracimab, a recombinant IgG1 monoclonal antibody that reverses the effect of ticagrelor, is safe and effective in promptly reversing the antiplatelet effect of ticagrelor among patients undergoing urgent surgery/procedure or with major bleeding (REVERSE-IT trial).

Contraindications:

- Patients with a high risk of bleeding, those with a history of intracranial haemorrhage, and those with severe hepatic dysfunction.

Cautions:

- It should be used with caution in those with acute asthma or COPD, as ticagrelor-treated patients experience higher rates of dyspnoea.
- Prespecified analysis of PLATO showed that the efficacy of ticagrelor appeared attenuated in those treated with higher doses of aspirin. As a result, FDA approval of ticagrelor for ACS was accompanied by a warning to avoid maintenance daily aspirin doses of more than 100 mg when using ticagrelor.

Pharmacological notes:

Unlike the thienopyridines, ticagrelor does not require metabolic activation or conversion for platelet inhibition; however, an active metabolite exerts an equally potent effect.

Due to its rapid absorption, plasma concentrations of ticagrelor peak 1-3 hours after oral administration in a dose-dependent manner. This results in an average of 60-80% inhibition of ADP-induced platelet aggregation 2-4 hours after a 180 mg loading dose. Plasma half life is 6-13 hours, necessitating twice daily administration. As compared to clopidogrel, ticagrelor results in earlier, more robust, and more consistent and pronounced platelet inhibition.

PAR-1 antagonists

Vorapaxar

Vorapaxar is an oral protease-activated receptor (PAR)–1 antagonist that inhibits thrombin-induced platelet activation by reversible binding of the PAR-1 receptor on platelets. Based on the small clinical benefit and increased risk of bleeding, vorapaxar has not been widely adopted in clinical practice.

Clinical evidence:

Table 36-6: Clinical trials of Vorapaxar:

| Trial (date) | Summary |
|------------------------------|--|
| TRACER (2012) | <i>In patients with ACS, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite endpoint of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization but significantly increased the risk of major bleeding, including intracranial hemorrhage.</i> |
| TRA 2P–TIMI 50 (2012) | <i>Vorapaxar reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis who were receiving standard therapy. However, it increased the risk of moderate or severe bleeding, including intracranial hemorrhage.</i> |

Intravenous Antiplatelet agents

Cangrelor

Clinical evidence:

Table 36-7: Clinical trials of Cangrelor:

| Trial (date) | Summary |
|--|--|
| The use of periprocedural cangrelor during PCI: | |
| CHAMION-PLATFORM (2009) | <i>In patients who had not been treated with clopidogrel at the time of PCI, the use of periprocedural cangrelor during PCI was not superior to placebo in reducing the composite of death, MI, or ischemia-driven revascularization at 48 hours. The stent thrombosis and death were lower in the cangrelor group, with no significant increase in the rate of transfusion.</i> |

**PHOENIX
(2013)**

In patients who were undergoing either urgent or elective PCI, cangrelor, as compared with clopidogrel, significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding.

Pharmacological notes:

Cangrelor is a rapid-acting, reversible, potent, competitive inhibitor of the P2Y₁₂ receptor. Given intravenously, cangrelor acts within 20 min to achieve 85% inhibition of ADP-induced platelet aggregation.

By whole blood impedance aggregometry there is 98% inhibition of platelet aggregation.

Cangrelor is rapidly deactivated in circulation by dephosphorylation to its primary metabolite, which has negligible antiplatelet activity. It is excreted in urine (58%) and feces (35%) with average half-life of 3-6 min.

Transition to an Oral P2Y₁₂ Receptor Antagonist:

When planning to transition from cangrelor to an oral P2Y₁₂ receptor antagonist, it is important for the clinician to know that cangrelor occupies the platelet P2Y₁₂ binding site, precluding the binding and pharmacodynamic effect of clopidogrel and prasugrel. Accordingly, these oral agents should be administered after cessation of cangrelor. By contrast, the binding site for ticagrelor is distinct allowing it to be administered during cangrelor administration.

GPIIb/IIIa receptor antagonists

Indications & clinical evidence:

There are currently three GPIIb/IIIa receptor antagonists: Abciximab, Tirofiban, and Eptifibatide.

Abciximab, a monoclonal antibody, is indicated for the prevention of ischemic cardiac complications in patients undergoing PCI and in patients presenting with unstable angina who are scheduled to undergo PCI.

Small-molecule GPIIb/IIIa receptor inhibitors, eptifibatide or tirofiban are indicated for the prevention of early MI in patients presenting with STEMI or unstable angina.

| Table 36-8: Clinical trials of Abciximab: | |
|---|---|
| Trial (date) | Summary |
| Abciximab: | |
| EPIC (1995) | <i>In patients undergoing either coronary angioplasty or atherectomy at high risk for thrombotic complications, abciximab reduced the occurrence of death, MI, or the need for an urgent intervention (repeat angioplasty, stent placement, IABP insertion, or bypass grafting) by 35%.</i> |
| EPILOG (1997) | <i>In patients undergoing elective or urgent percutaneous coronary revascularization, abciximab together with low-dose, weight-adjusted heparin, markedly reduces the risk of acute ischemic complications, without increasing the risk of hemorrhage.</i> |
| CAPTURE (1997) | <i>In patients with refractory unstable angina, treatment with abciximab substantially reduces the rate of thrombotic complications, in particular MI, before, during, and after PTCA. There was no evidence that this regimen influenced the rate of MI after the first few days, or the need for subsequent reintervention.</i> |
| GUSTO V (2002) | <i>In patients with acute STEMI, there were fewer nonfatal ischemic complications of MI with reteplase plus abciximab compared with reteplase alone. 30-day mortality and intracranial hemorrhage rates did not differ between treatments; however, moderate-to-severe bleeding was more likely with combined therapy, and patients > 75 years of age were at increased risk for hemorrhagic stroke.</i> |
| ISAR-REACT 2 (2006) | <i>In NSTEMI patients scheduled to undergo PCI, abciximab on top of a background therapy of 600 mg of oral clopidogrel loading demonstrated a reduction in the primary composite endpoint of 30-day death, MI, or urgent revascularization without an increase in major or minor bleeding.</i> |
| Tirofiban: | |

| | |
|-----------------------------|--|
| RESTORE (1997) | <i>In patients with ACS undergoing PCI, tirofiban protects against early adverse cardiac events related to thrombotic closure. At 30 days, however, the reduction in adverse cardiac events was no longer statistically significant. Bleeding observed with tirofiban was not statistically different from that observed with placebo.</i> |
| PRISM (1998) | <i>In patients with NSTEMI-ACS, tirofiban, if administered with heparin and aspirin, was associated with a lower incidence of ischemic events than in patients who received only heparin and aspirin.</i> |
| Eptifibatide: | |
| PURSUIT (1998) | <i>In patients with NSTEMI-ACS, eptifibatide infusion, in addition to standard therapy, for up to 72 hrs (or up to 96 hrs, if coronary intervention was performed near the end of the 72-hr period) reduced the incidence of the composite end point of death or nonfatal MI.</i> |
| ESPRIT (2000) | <i>The trial was terminated early for efficacy. Patients receiving eptifibatide prior to PCI had a 4.0% absolute reduction in death, MI, urgent target vessel revascularization, or “bailout” GPIIb/IIIa antagonist use within 48 hrs compared with placebo. Major events were lower at 30 days.</i> |
| EARLY-ACS (2009) | <i>In patients who had NSTEMI-ACS and who were assigned to an invasive strategy, the use of eptifibatide 12 hrs or more before angiography was not superior to the provisional use of eptifibatide after angiography. The early use of eptifibatide was associated with an increased risk of non-life-threatening bleeding and need for transfusion.</i> |

Anticoagulant

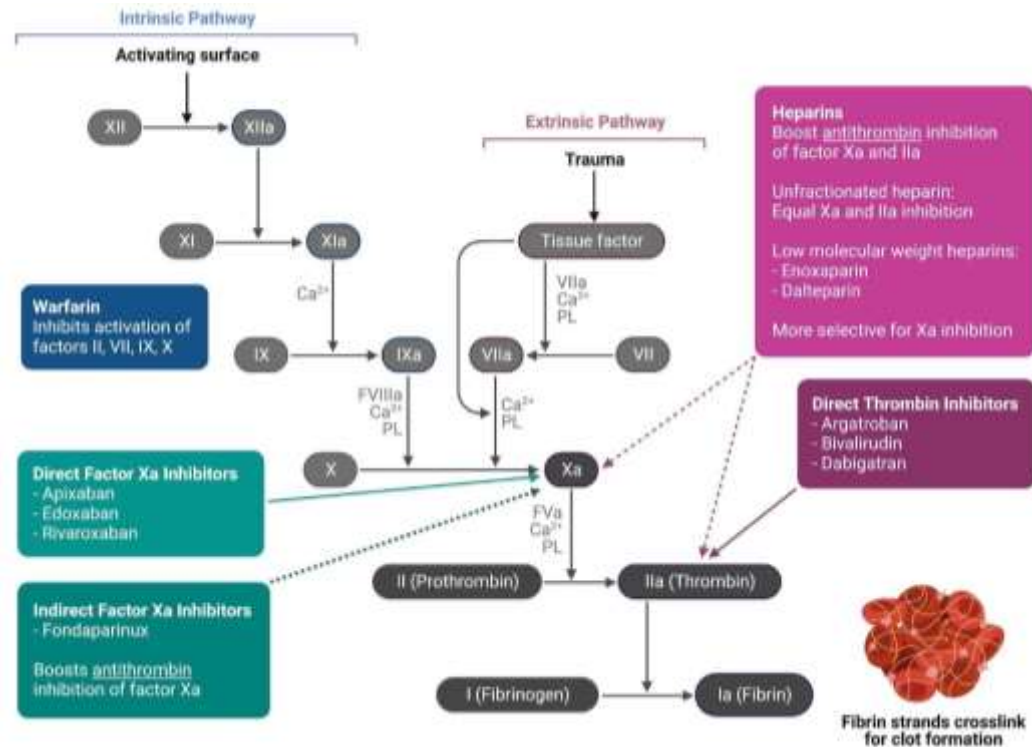


Figure 36-2: Anticoagulation treatments: pharmacological targets.

Oral Anticoagulants

Vitamin K antagonist (Warfarin)

Mechanism of action:

Warfarin is an oral anticoagulant which inhibits epoxide reductase preventing the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C and S. S-warfarin is 4 times more potent than R-warfarin.

Indications & clinical evidence:

- Venous thromboembolism: target INR = 2.0-3.0, if recurrent 3.5:
 - Treatment duration of 3 months: surgery-provoked VTE, transient (reversible) risk factor-induced VTE, first unprovoked proximal VTE with high bleeding risk, first unprovoked distal DVT regardless of bleeding risk, second unprovoked VTE with high bleeding risk.
 - Extended treatment: First unprovoked proximal VTE with low or moderate bleeding risk, Second unprovoked VTE with low or moderate bleeding risk.
- Atrial fibrillation, target INR = 2.0-3.0
- Mechanical heart valves, target INR depends on the valve type and location:
 - Mitral bioprosthetic valve: INR 2.0-3.0 for 3-months. If other risk factors for thromboembolism (AF, previous thromboembolism, LV dysfunction), longer duration may be necessary.
 - Aortic mechanical valve: INR 2.0-3.0 for indefinite treatment duration.
 - Mitral mechanical, or both aortic and mitral mechanical valves: INR 2.5-3.5 for indefinite duration.

Adverse effects:

- Haemorrhage

- Teratogenic, although can be used in breastfeeding mothers.
- Skin necrosis: when warfarin is initially started, biosynthesis of protein C is reduced, which results in a temporary procoagulant state, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis.
- Purple toes
- Calciphylaxis (serious, uncommon disease in which calcium accumulates in small blood vessels of the fat and skin tissues) or calcium uremic arteriopathy has been reported in patients with and without ESRD; discontinue warfarin and treat calciphylaxis as appropriate; consider alternative anticoagulant.

Contraindications:

- Pregnancy, except in women with mechanical heart valves
- Hemorrhagic tendencies or blood dyscrasias
- Recent or contemplated CNS or eye surgery or traumatic surgery resulting in large open surfaces
- Patients with conditions associated with high level of non-compliance (eg, dementia, alcoholism)
- Spinal puncture with potential for uncontrollable bleeding
- Known hypersensitivity.
- Malignant hypertension

Cautions:

Factors that may potentiate warfarin:

- Liver disease
- Thyroid disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- Cranberry juice

- Drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- Inhibit platelet function: NSAIDs

Monitoring:

Patients on warfarin are monitored using the INR, the ratio of the prothrombin time for the patient over the normal prothrombin time. Warfarin has a long half-life and achieving stable INR may take several days.

| Table 36-9: Maintenance Warfarin dosing for out-of therapeutic-range INR: | |
|---|--|
| INR | Dose adjustment per week |
| ≤ 1.5 | ↑ by 15%/week |
| 1.6-1.9 | ↑ by 10%/week |
| 2-2.9 | Unchanged |
| 3-3.9 | ↓ by 10%/week |
| 4-4.9 | Hold 1 dose, then restart with dose ↓ by 10%/week |
| ≥ 5 | Hold until INR is 2–3, then restart with dose ↓ by 15%/week. |

Management of high INR:

| Table 36-10: Management of high INR in patients on warfarin therapy (BNF guidelines): | |
|---|--|
| Situation | Management |
| Major bleeding | <ul style="list-style-type: none"> - Stop warfarin - Give i.v. vitamin K 5 mg - Prothrombin complex concentrate - if not available then FFP |
| INR > 8.0 | |

| | |
|-----------------------|--|
| Minor bleeding | <ul style="list-style-type: none"> - Give i.v. vitamin K 1-3 mg - Repeat dose of vitamin K if INR still too high after 24 hrs - Restart warfarin when INR < 5.0 |
| No bleeding | <ul style="list-style-type: none"> - Give vitamin K 1-5 mg by mouth, using the i.v. preparation orally - Repeat dose of vitamin K if INR still too high after 24 hours - Restart warfarin when INR < 5.0 |
| INR 5.0-8.0 | |
| Minor bleeding | <ul style="list-style-type: none"> - Give i.v vitamin K 1-3mg - Restart warfarin when INR < 5.0 |
| No bleeding | <ul style="list-style-type: none"> - Withhold 1 or 2 doses of warfarin - Reduce subsequent maintenance dose. |

Non-vitamin K antagonist oral anticoagulants

Pharmacological features:

Table 36-11: Pharmacological features of NOACs:

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|----------------------------------|---------------------------------|--|-----------|--------------------------------|
| Mechanism | Direct thrombin (IIa) inhibitor | Direct factor Xa inhibitor | | |
| Bioavailability | 6% | 80-100% with food (<i>Intake with food is mandatory</i>) | 50% | 62% |
| Time to peak, hrs | 3 | 2-4 | 3 | 1-2 |
| Prodrug | Yes | No | No | No |
| Half-life, hrs | 12-17 | 5-13 | 9-14 | 10-14 |
| Renal Clearance | 80% renal | 65% liver, 35% renal | 25% renal | 50% renal |
| Dialysability | 50-60% | N.A. | 14% | N.A. |
| Plasma protein binding | 35% | 95% | 87% | 55% |
| Liver metabolism (CYP3A4) | No | Yes (Elimination, moderate contribution) | | Minimal |
| Drug transporters | Substrate P-glycoprotein (P-gp) | Substrate P-gp Substrate ABCG2 | | Substrate P-gp Substrate ABCB1 |
| Not recommended | CrCl < 30 mL/min | CrCl < 15 mL/min | | |
| Antidote | Idarucizumab 5 g | Andexanet alpha (400 mg over 15 min, followed by 4 mg/min for 2 hrs) | | |

Indications and Clinical evidence:

- **Dabigatran:**

| Table 36-12: Clinical trials of Dabigatran: | |
|---|---|
| Trial (date) | Summary |
| Venous thromboembolism: | |
| RE-Cover (2009) | <i>In patients with acute venous thromboembolism who were initially given parenteral anticoagulation therapy for a median of 9 days, a fixed dose of dabigatran is as effective as warfarin and has a safety profile that is similar to that of warfarin.</i> |
| RE-MEDY (2013) | <i>In patients with venous thromboembolism who had completed at least 3 initial months of therapy, Dabigatran was effective in the extended treatment of venous thromboembolism and carried a lower risk of major or clinically relevant bleeding than warfarin but higher risk than placebo.</i> |
| RESONATE (2013) | |
| Atrial Fibrillation: | |
| RE-LY (2009) | <i>In patients with nonvalvular AF and a mean CHADS2 score of 2.1, Dabigatran was associated with rates of stroke and systemic embolism similar to those associated with warfarin, as well as lower rates of major hemorrhage.</i> |
| Ablation: | |
| RE-CIRCUIT (2017) | <i>In patients scheduled for catheter ablation for paroxysmal or persistent AF, which was performed after 4-8 weeks of uninterrupted anticoagulation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin.</i> |

- **Rivaroxaban:**

| Table 36-13: Clinical trials of Rivaroxaban: | |
|--|--|
| Trial (date) | Summary |
| Venous thromboembolism: | |
| EINSTEIN DVT (2010) | <i>In patients with acute DVT, Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation.</i> |
| EINSTEIN PE (2012) | <i>In patients who had acute symptomatic pulmonary embolism with or without DVT, Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism.</i> |
| Atrial Fibrillation: | |
| ROCKET-AF (2011) | <i>In patients with nonvalvular AF who were at increased risk for stroke, rivaroxaban (at a daily dose of 20 mg) was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.</i> |
| Atrial Fibrillation and PCI: | |
| PIONEER AF-PCI (2016) | <i>In patients with nonvalvular AF who had undergone PCI with stenting, the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT.</i> |
| Heart Failure: | |
| COMMANDER-HF (2018) | <i>In patients who had at least a 3-month history of chronic heart failure, LVEF \leq 40%, and coronary artery disease and who had been treated for an episode of worsening heart failure within the previous 21</i> |

| | |
|---------------------------------------|---|
| | <i>days, rivaroxaban (2.5 mg twice daily) was not associated with a significantly lower rate of death, MI, or stroke than placebo.</i> |
| Stable Cardiovascular Disease: | |
| COMPASS (2017) | <i>In patients with stable atherosclerotic vascular disease, rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events.</i> |
| Ablation: | |
| VENTURE-AF (2015) | <i>Patients with Non valvular AF undergoing CA, the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.</i> |

- **Apixaban:**

| Table 36-14: Clinical trials of Apixaban: | |
|--|--|
| Trial (date) | Summary |
| Venous thromboembolism: | |
| AMPLIFY (2013) | <i>In patients with acute venous thromboembolism, Apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) was noninferior to conventional therapy and was associated with significantly less bleeding.</i> |
| Atrial Fibrillation: | |
| ARISTOTLE (2011) | <i>In patients with AF and at least one additional risk factor for stroke, Apixaban (5 mg twice daily) was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.</i> |

| | |
|---------------------------|--|
| AUGUSTUS (2019) | <i>In patients with AF who had an ACS or had undergone PCI and were planning to take a P2Y12 inhibitor, antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.</i> |
| Ablation: | |
| AXAFA-AFNET (2018) | <i>In patients with AF at risk of stroke and underwent ablation, apixaban (5 mg b.i.d.) is safe and effective with respect to bleeding, stroke, and cognitive function.</i> |

- **Edoxaban:**

| Table 36-15: Clinical trials of Edoxaban: | |
|--|---|
| Trial (date) | Summary |
| Venous thromboembolism: | |
| Hokusai-VTE (2013) | <i>In patients with acute venous thromboembolism, including those with severe pulmonary embolism, Edoxaban administered once daily after initial treatment with heparin was noninferior to standard therapy and caused significantly less bleeding.</i> |
| Atrial Fibrillation: | |
| ENGAGE AF-TIMI 48 (2013) | <i>In patients with moderate-to-high-risk AF, edoxaban was noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.</i> |

Doses:

| Table 36-16: Dosing of NOACs: | | | |
|--|--|--|---|
| Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
| Stroke prevention in AF: | | | |
| 2 x 150 mg | 1 x 20 mg | 2 x 5 mg | 1 x 60 mg |
| 2 x 110 mg if: <ul style="list-style-type: none"> - Age ≥ 80 years. - Concomitant verapamil. - Increased risk of GI bleeding. | 1 x 15 mg if CrCl ≤ 50 mL/min | 2 x 2.5 mg if: <ul style="list-style-type: none"> ○ If CrCl 15-29 mL/min ○ Or two out of three: <ul style="list-style-type: none"> - BW ≤ 60 kg, - Age ≥ 80 years - S. Cr. ≥ 1.5 mg/dL | 1 x 30 mg if: <ul style="list-style-type: none"> BW ≤ 60 kg, CrCl ≤ 50 mL/min, concomitant therapy with strong P Gp inhibitor |
| Treatment of DVT/PE: | | | |
| Heparin/LMWH <u>then</u> 2 x 150 mg | 2 x 15 mg for 21 days <u>then</u> 1 x 20 mg | 2 x 10 mg for 7 days <u>then</u> 2 x 5 mg | Heparin/LMWH <u>then</u> 1 x 60 mg |
| Long-term prevention of recurrent DVT/PE (i.e. after 6 months): | | | |
| 2 x 150 mg | 1 x 10 mg | 2 x 2.5 mg | Not specifically studied |
| VTE prevention post-major orthopaedic surgery: | | | |
| 1 x 220 mg | 1 x 10 mg | 2 x 2.5 mg | 1 x 30 mg |
| Stroke prevention post-PCI (with concomitant AF): | | | |
| 150 mg BID or 110 mg BID + Clopidogrel or Ticagrelor | 15 mg OD (+ Clopidogrel) | 2 x 5 mg (+ Clopidogrel) | 60 mg daily + clopidogrel |

| | | | |
|--|--|------------------------|--|
| Secondary prevention of atherothrombotic events post-ACS/stable CAD (without AF): | | | |
| | | 2.5 mg BID (+ Aspirin) | |

| | | | |
|--|--|------------------------|--|
| | | 2.5 mg BID (+ Aspirin) | |
|--|--|------------------------|--|

Use in liver and renal impairment:

Table 36-17: use of NOACs in hepatic insufficiency:

| Child-Pugh Category | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---------------------|-------------------|-------------|----------------|----------------|
| A (5-6 points) | No dose reduction | | | |
| B (7-9 points) | Use with caution | Do not use | Use cautiously | Use cautiously |
| C (10-15 points) | Do not use | | | |

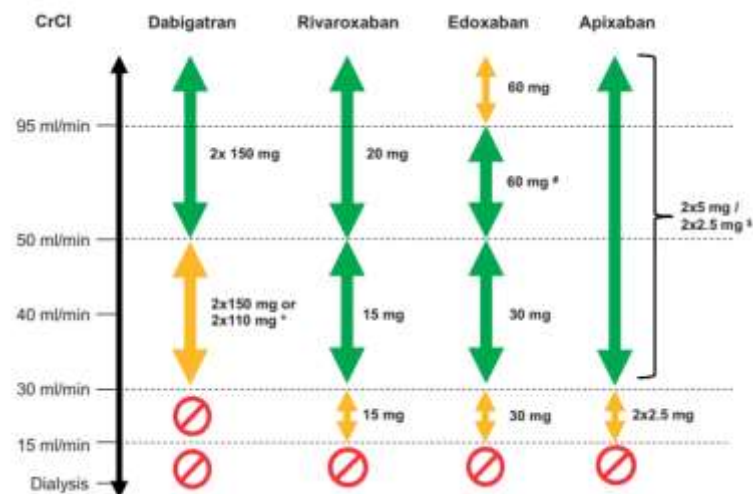


Figure 36-3: Use of non-vitamin K antagonist oral anticoagulants according to renal function. * 2x110mg in patients at high risk of bleeding (per SmPc). # Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). § 2x 2.5mg only if at least two out of three fulfilled: age ≥ 80 years, body weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL (133 mmol/L). **Orange arrows** indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function). **Source:** Hasenfuss, G. and Teerlink, J.R., 2011. Cardiac inotropes: current agents and future directions. European heart journal, 32(15), pp.1838 1845.

Adverse effects:

- **Major bleeding:** Dabigatran= 3.47% (vs 3.58% in warfarin), Apixaban= 2.13% (vs 3.09% in warfarin), Edoxaban= 3.1% (vs 3.7% in warfarin).
- **GI bleeding:** Dabigatran= 1.59% (vs 1.51% in warfarin), Apixaban= 0.83% (vs 0.93% in warfarin).
- **Intracranial hemorrhage:** Dabigatran= 0.22% (vs 0.77% in warfarin), Apixaban= 0.33% (vs 0.82% in warfarin), Edoxaban= 0.5% (vs 1% in warfarin).
- **Fatal hemorrhage:** Apixaban= 0.06% (vs 0.24% in warfarin), Edoxaban= 1.8% (vs 0.4% in warfarin).

Drug interactions:

Coadministration with both inducers (rifampin) of P-gp and inhibitors of P-gp (e.g., ketoconazole, amiodarone, verapamil, quinidine) results in considerable changes in NOACs exposure, C_{\max} and AUC.

Current recommendations include a reduction in NOACs dose when coadministered with drugs that are strong dual inhibitors of CYP 3A4 and P-gp (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin).

Perioperative management of NOACs:

Table 36-18: Last intake of drug before elective surgical intervention:

| | Dabigatran | | Apixaban—Edoxaban—Rivaroxaban | |
|---|--|-------------|-------------------------------|-------------|
| | <i>No important bleeding risk and/or adequate local hemostasis possible: perform at trough level (i.e. ≥ 12 or 24 h after last intake)</i> | | | |
| | Low risk | High risk | Low risk | High risk |
| CrCl ≥ 80 mL/min | ≥ 24 h | ≥ 48 h | ≥ 24 h | ≥ 48 h |
| CrCl 50-80 mL/min | ≥ 36 h | ≥ 72 h | | |
| CrCl 30-50 mL/min | ≥ 48 h | ≥ 96 h | | |
| CrCl 15-30 mL/min | Not indicated | | ≥ 36 h | |
| CrCl < 15 mL/min | <i>No official indication for use</i> | | | |
| There is no need for bridging with LMWH/UFH | | | | |
| Resume full dose ≥ 24 h post-low bleeding risk interventions and 48-72 h post-high-bleeding risk interventions | | | | |

How to deal with dosing errors?

○ Missed dose:

A forgotten dose may be taken until 50% of the dosing interval has passed. For patients with a high stroke risk and low bleeding risk, this may be extended up until the next scheduled dose. For NOACs with an OD dosing regimen, a forgotten dose can be

taken up until 12 h after the scheduled intake. After this time point, the dose should be skipped and the next scheduled dose should be taken.

○ **Double dose:**

For NOACs with a BID dosing regimen, the next planned dose (i.e., after 12 h) may be left out, with BID intake restarted 24 h after the double dose intake. For NOACs with an OD dosing regimen, the patient should continue the normal dosing regimen, i.e., without skipping the next daily dose.

○ **Uncertainty about dose intake:**

For NOACs with a BID dosing regimen, it is generally advisable to not take another tablet/capsule, but to simply continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval.

For NOACs with an OD dosing regimen, when thrombotic risk is high ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 3$), it may generally be advisable to take another tablet and then continue the planned dose regimen. In case the thrombotic risk is low ($\text{CHA}_2\text{DS}_2\text{-VASc} \leq 2$), it is recommended to wait until the next scheduled dose.

Comparison to warfarin:

Table 36-19: Comparison of NOACs to warfarin in AF:

| Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|--|---|---|---|
| <ul style="list-style-type: none"> ○ ↓ ischemic stroke ○ ↓ intracranial hemorrhage (%70~) ⁽¹⁾ ○ Same major bleeding ○ ↓ death (~0.5%/yr) ○ ↑ GI bleeding | <ul style="list-style-type: none"> ○ Same ischemic stroke ○ ↓ intracranial hemorrhage ○ Same major bleeding ○ ↓ death trend | <ul style="list-style-type: none"> ○ Same ischemic stroke ○ ↓ intracranial hemorrhage (%50~) ○ ↓ major bleeding ○ ↓ death ○ No ↑ GI bleeding | <ul style="list-style-type: none"> ○ ↑ ischemic stroke if GFR > 95 ml/min (excessive drug clearance), same ischemic stroke if GFR < 95 ml/min ○ ↓ intracranial hemorrhage ○ ↓ major bleeding |

(1) The selective inhibition of the clotting cascade and the lack of inhibition of the extrinsic pathway (factor VII) explain the reduction of intracranial hemorrhage with all of these agents.

| | | | |
|--|-----------------|--|-----------------------------------|
| | ○ ↑ GI bleeding | | ○ ↓death trend ○ ↑ GI bleeding |
|--|-----------------|--|-----------------------------------|

Parenteral anticoagulation

Table 36-20: Pharmacokinetic characteristics of parenteral anticoagulants

| | Unfractionated heparin | Enoxaparin | Dalteparin | Fondaparinux | Bivalirudin | Argatroban |
|--------------------------------------|--|------------|------------|----------------------------|---|---|
| Target | AT | AT | AT | AT | Thrombin | Thrombin |
| Bioavailability | Unpredictable | 90-92% | 87% | 100% | 40-80% | 100% |
| Vd | 40-70 mL/min | 4.3 L | 3-4 L | 7-11 L | 0.24 L/Kg | 0.174 L/kg |
| Protein binding | > 90% | < UFH | < UFH | 94% specifically to ATIII | No plasma proteins; just thrombin | 55% 20% albumin 35% α -acid glycoprotein |
| Time to peak activity (hours) | Rapid after bolus, 4-6 h after infusion | 3-5 h (SQ) | 2-4 h(SQ) | 2-3 h (SQ) | 2 min after bolus; 4 min after 15 min infusion | 3-4 h after infusion |
| Half-life (hours) | 1.0-1.5 | 5.0 | 3-5 | 17 (young) 21 (elderly) | 0.5 | 0.5-1.0 |
| Elimination | Primarily by reticuloendothelial system | 80% Renal | Renal | Renal | Renal and proteolytic cleavage | Hepatic hydroxylation; 16% renal 14% biliary |
| CYP metabolism | No | No | No | No | No | Yes |
| CYP isoenzymes | No | No | No | No | No | CYP 3A4/5 |

Unfractionated Heparin

Mechanism of action:

UFH exerts its anticoagulant effects in three well-characterized and distinct ways.

- The major anticoagulant effect is the result of its high affinity for AT and the conformational change in AT that occurs from the binding of heparin and AT, inactivating FIXa, FXa, FXIa, and FXIIa.
- The second mechanism of UFH's anticoagulant effect is inactivation of thrombin by heparin cofactor II.

The third mechanism that may not be clinically relevant at expected drug concentrations is through modulation of FXa generation achieved by UFH binding to factor IXa.

Indications and Clinical evidence:

• DVT & PE:

- Prophylaxis: 5000 units SC q8-12hr, OR 7500 units SC q12hr
- Treatment: 80 units/kg IV bolus, THEN continuous infusion of 18 units/kg/hr

- **Acute Myocardial Infarction:** In acute MI STEMI, UFH can be administered with thrombolytic therapy or during primary PCI. Patient on fibrinolytics: IV bolus of 60 units/kg (max: 4000 units), THEN 12 units/kg/hr (max 1000 units/hr) as continuous IV infusion (adjusted to maintain aPTT of 50-70 sec).

- **Elective PCI:** (Heparin should be discontinued immediately after PCI).

- Without GPIIb/IIIa inhibitor: Initial IV bolus of 70-100 units/kg (target ACT 250-300 sec).
- With GPIIb/IIIa inhibitor: Initial IV bolus of 50-70 units/kg (target ACT > 200 sec).

- **Extracorporeal Membrane Oxygenation (ECMO):** Blood exposure to the large surface of the ECMO circuits disrupts normal hemostasis like other MCS devices but also induces a strong inflammatory response similar to cardiopulmonary bypass. In the absence of HIT, anticoagulation with UFH is necessary to prevent clotting of the ECMO circuit with a goal aPTT 1.5-2.0 times the upper limit of normal.

- **LVAD thrombosis:** Standard treatment for suspected or confirmed pump thrombosis is anticoagulation with IV UFH and the addition of antiplatelet therapy. Direct thrombin inhibitors, primarily bivalirudin, have been used as an alternative anticoagulant to UFH.

Adverse effects:

- Bleeding and HIT are the most common and feared complications of UFH administration. It occurs due to the development of antibodies to a platelet Factor 4-heparin complex that induce in vivo platelet aggregation.
- Other adverse effects include hypersensitivity reactions, adrenal hemorrhage with shock, and osteopenia (with long-term administration).

HIT Therapy:

Lepirudin, argatroban, and bivalirudin can be used in the management of HIT. In patients with suspected or proven HIT who require PCI, argatroban (direct thrombin inhibitor, 240 µg/kg bolus followed by 20 µg/kg/min infusion) can be used during the intervention, with or without a GPIIb/IIIa antagonist. Bivalirudin is licensed for use when HIT or heparin induced thrombocytopenia and thrombosis syndrome (HITS) complicates PCI.

Contraindications:

- History of Heparin-induced thrombocytopenia (HIT) (with or without thrombosis)
- Uncontrolled, active bleeding (except DIC)
- Conditions in which coagulation tests cannot be performed at appropriate intervals.
- Known hypersensitivity to heparin or pork products.

Reversal and Replacement Therapy:

For unfractionated heparin, protamine sulfate (12.5-50 mg IV) is the drug of choice. It is strong half-life protein forming a strong bond with the heparin producing an inactive complex. 1 mg protamine sulfate will neutralize 100 units of UFH.

Cautions:

- Heparin resistance may be observed in patients with antithrombin deficiency, increased heparin clearance, elevations of heparin binding proteins, elevations of factor VIII and/or fibrinogen and may require doses > 35,000 units/24hr to maintain therapeutic aPTT; may benefit from measurements of anticoagulant effects using antifactor Xa levels.
- Monitor therapy with aPTT, but heparin may prolong PT.

Low-Molecular-Weight Heparins

(Enoxaparin, Dalteparin, Tinzaparin and Nadroparin)

Mechanism of action:

LMWH inhibits coagulation by activating antithrombin III. Antithrombin III binds to and inhibits factor Xa. In doing so, it prevents activation of the final common path; Xa inactivation means that prothrombin is not activated to thrombin, thereby not converting fibrinogen into fibrin for the formation of a clot.

Indications and Clinical evidence:

- **DVT prophylaxis** in patients at risk undergoing abdominal surgery or hip or knee replacement surgery, as well as patients with severely restricted mobility during acute illness (40 mg SC qDay).
- **Treatment of acute DVT with or without PE**, when administered in conjunction with warfarin (1 mg/kg SC q12hr, OR 1.5 mg/kg SC qDay).
- **Treatment of STEMI** (in both those undergoing PCI and those not):
 - **< 75 years:** Loading dose: 30 mg IV bolus once plus 1 mg/kg SC once; not to exceed 100 mg cumulative loading dose. Maintenance: 1 mg/kg SC q12hr.
 - **> 75 years:** 0.75 mg/kg SC q12hr (No IV bolus).
 - **With PCI:** 0.5-0.75 mg/kg bolus dose
 - If last enoxaparin was given <8 hr before balloon inflation: no additional dosing.
 - If last enoxaparin was given 8-12 hr before balloon inflation: IV bolus of 0.3 mg/kg.
 - If PCI occurs >12 hr after last SC dose: full-dose unfractionated heparin or LMWH
- **Treatment of NSTEMI-ACS:** Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin (1 mg/kg SC q12hr).
- **Prevention of clotting in extracorporeal circuits.**

Table 36-21: Clinical trials of LMWH:

| Trial (date) | Summary |
|-------------------------------|--|
| NSTE-ACS: | |
| FRIC (1997) | <i>In patients with unstable angina or non-Q-wave MI, subcutaneous dalteparin (120 i.u./kg) may be an alternative to unfractionated heparin in the acute treatment.</i> |
| FRISC II (1999) | <i>In patients with unstable coronary artery disease, dalteparin lowers the risk of death, MI, and revascularization in unstable coronary-artery disease at least during the first month of therapy.</i> |
| ESSENCE (1997) | <i>In patients with angina at rest or non-Q-wave MI, antithrombotic therapy with enoxaparin plus aspirin was more effective than unfractionated heparin plus aspirin in reducing the incidence of ischemic events in the early phase. This benefit of enoxaparin was achieved with an increase in minor but not in major bleeding.</i> |
| TIMI IIB (1998) | <i>In patients with unstable angina and NSTEMI, enoxaparin was associated with a significant reduction in the composite outcome of death, MI or urgent revascularization compared with UFH at day 14. Continued treatment beyond the initial hospital phase did not provide added benefit.</i> |
| SYNERGY (2004) | <i>In high-risk NSTE-ACS patients, enoxaparin was not superior to unfractionated heparin but was noninferior for the treatment of those patients. Enoxaparin is a safe and effective alternative to unfractionated heparin with the modest excess of major bleeding.</i> |
| STEMI: | |
| ExTRACT-TIMI 25 (2006) | <i>In patients with STEMI, treatment with enoxaparin throughout the index hospitalization is superior to treatment with unfractionated heparin for 48 hours but is associated with an increase in major bleeding episodes.</i> |
| ATOLL (2011) | <i>In patients presenting with STEMI, i.v. enoxaparin compared with unfractionated heparin significantly reduced clinical ischemic outcomes without differences in bleeding and procedural success. Therefore, enoxaparin provided an improvement in net clinical benefit in patients undergoing primary PCI.</i> |

Adverse effects:

The main risk of LMWH will be bleeding.

Less common adverse effects include: HIT, osteoporosis, spontaneous fractures, hypoaldosteronism, hypersensitivity reactions, elevation of serum aminotransferases (6%) and Fever (5-8%).

Reversal and Replacement Therapy:

For LMWH, protamine sulfate (0.5–1.0 mg for every 1 mg of LMWH given within the past 8 hours) is recommended. It is important to recognize that protamine sulfate will neutralize approximately 40-50% of LMWH-specifically the factor IIa effect. Prothrombin complex concentrate (PCC) can be given for refractory bleeding.

Contraindications:

- Active major bleeding.
- Thrombocytopenia with antiplatelet antibody in presence of enoxaparin or heparin
- History of HIT within past 100 days or in presence of circulating antibodies
- Hypersensitivity to enoxaparin, heparin, pork products, benzyl alcohol.

Cautions:

- Administer deep SC alternating right and left anterior and posterior abdominal walls into skin fold held between thumb and forefinger.
- For IV administration, may administer in IV line with 0.9% NaCl or D5W.

Pharmacological notes:

LMWHs are derived from UFH by chemical depolymerization. The overall process creates fragments that are approximately one-third the molecular weight of UFH. These short chains do promote FXa inhibition, and accordingly LMWHs are comparatively

more selective inhibitors of FXa than UFH. Other favorable features of LMWHs from UFH include reduced protein binding that improves their pharmacokinetic properties and results in a more predictable anticoagulant response and reduced interaction with platelets, which reduces the likelihood of heparin-induced thrombocytopenia (HIT).

The LMWH-AT complex has relatively weak AT activity but retains the ability to inactivate FXa. The ratio of anti-Xa activity to anti-IIa (antithrombin) activity varies from 2:1 to 4:1. Similar to UFH, LMWH does not inhibit thrombin bound to fibrin.

When LMWH is given in either fixed or weight-adjusted doses by the SQ route, greater than 90% of the dose is absorbed. By contrast to UFH, LMWH has minimal binding to cells or plasma proteins, resulting in persistence of free drug in the circulation and a longer half-life. While the half-life of UFH averages about 90 minutes, the half-life of LMWH averages about 180 minutes (the half-lives of three LMWHs range from 90 to 260 minutes).

Direct Thrombin Inhibitors

(Hirudin, Bivalirudin and Argatroban)

DTIs interact directly with thrombin and do not require AT (or heparin cofactor II) to achieve an anticoagulant effect. They specifically and reversibly inhibit free and clot-bound thrombin by binding to the active site of thrombin. Hirudin was used for the first parenteral anticoagulation in humans in 1909 and as the anticoagulant for the first hemodialysis in humans.

Indications and Clinical evidence:

Table 36-22: Clinical trials of Direct Thrombin Inhibitors:

| Trial (date) | Summary |
|-------------------------|---|
| Hirudin: | |
| | The first indication for which a hirudin -lepirudin- has been approved is treatment of heparin-induced thrombocytopenia (HIT). Also, the recently completed trials for use of lepirudin in unstable angina indicate a potentially new indication. |
| GUSTO IIb (1998) | <i>In patients with NSTEMI-ACS, hirudin reduced the 24-hr risk of death or nonfatal MI, as compared to UFH. The risk of moderate bleeding was increased with hirudin treatment.</i> |

| | |
|--|--|
| OASIS-1 (1999) | <i>In patients with NSTEMI-ACS, hirudin, compared to UFH, reduced the composite incidence of cardiovascular death, MI, or refractory angina at 7 days and a composite of death, MI, or refractory/severe angina requiring revascularization at 7 days.</i> |
| OASIS-2 (2001) | <i>In patients with NSTEMI-ACS, there is no statistically significant differences between hirudin and UFH. The combined OASIS-1 and OASIS-2 experience revealed a significant reduction in the likelihood of death or MI at 3-5 days among hirudin-treated patients.</i> |
| Bivalirudin: | |
| Bivalirudin is indicated for IV anticoagulation in patients with acute MI, unstable angina, PCI, and thrombosis in patients with a history of HIT. More recently, bivalirudin has been explored and utilized off-label in patients undergoing cardiopulmonary bypass and ECMO and for DVT prophylaxis. | |
| REPLACE-2 (2003) | <i>In patients undergoing urgent or elective PCI, bivalirudin with provisional GPIIb/IIIa blockade is statistically not inferior to heparin plus planned GPIIb/IIIa blockade during contemporary PCI with regard to suppression of acute ischemic end points and is associated with less bleeding.</i> |
| HORIZONS-AMI (2008) | <i>In patients undergoing planned primary PCI for acute STEMI, anticoagulation with bivalirudin alone, as compared with heparin plus GPIIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events.</i> |

Reversal and Replacement Therapy:

The approach to parenteral direct thrombin inhibitors, in addition to supportive measures, includes PCC and recombinant FVII for refractory bleeding. The use of idarucizumab, a reversal agent specifically designed to reverse dabigatran's anticoagulant effect, is not recommended and would not be expected to have an effect.

Direct FXa Inhibitors (Fondaparinux)

Mechanism of action:

Selectively bind to antithrombin III, thereby potentiating the innate neutralization of activated factor X (Factor Xa) by antithrombin. Neutralization of Factor Xa inhibits its activity and interrupts the blood coagulation cascade, thereby preventing thrombin formation and thrombus development. It generally does not increase PT or PTT.

Indications and Clinical evidence:

Table 36-23: Clinical trials of fondaparinux:

| Trial (date) | Summary |
|---|--|
| Acute coronary syndrome: | |
| OASIS-5 (2006) | <i>In patients with ACS, fondaparinux was associated with a significant reduction in the number of patients with fatal bleeding and TIMI major bleeding.</i> |
| OASIS-6 (2006) | <i>In patients with STEMI, fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes.</i> |
| Deep Vein Thrombosis/Acute Pulmonary Embolism: | |

- **Treatment: Administer for 5-9 days; up to 26 days**
 - < 50 kg: 5 mg SC once daily
 - 50-100 kg: 7.5 mg SC once daily
 - > 100 kg: 10 mg SC once daily
- **Prophylaxis: > 50 kg: 2.5 mg SC once daily for 5-9 days or up to 10 days (following abdominal surgery); 11 days (for hip replacement), 10-14 days (for total hip or knee arthroplasty).**

Adverse effects:

- Anemia (1-20%).
- Fever (4-14%).
- Edema (9%).
- Rash (7.5%).
- Dizziness (4%).
- Constipation (5-9%).
- Diarrhea (2-3%).
- Headache (2-5%).
- Hypokalemia (1-4%).

Reversal and Replacement Therapy:

Andexanet alfa was designed as a universal FX anticoagulant reversal agent, including fondaparinux.

Contraindications:

- Severe renal impairment (CrCl < 30 mL/min)
- Body weight < 50 kg (venous thromboembolism prophylaxis only)

- Active major bleeding
- Bacterial endocarditis.
- Thrombocytopenia with antiplatelet antibody in presence of fondaparinux.
- History of serious hypersensitivity reaction (e.g., angioedema, anaphylactoid or anaphylactic reactions).

Cautions:

- Epidural or spinal hematomas may occur in patients undergoing anticoagulation with LMWHs or heparinoids who receive neuraxial (epidural or spinal) anesthesia. These hematomas may result in long-term or permanent paralysis. Patients should be monitored for signs of neurologic impairment.
- May cause prolonged anticoagulation in moderate renal impairment (CrCl 30-50 mL/min).
- Discontinue if platelets <100,000/ μ L.
- Not for IM administration.
- Do not use interchangeably with heparin or LMWHs.
- Do not administer initial dose earlier than 6-8 hours after surgery; administration earlier than 6 hours after surgery increases risk of major bleeding.
- Increased risk of bleeding in patients < 50 kg; dosage reduction recommended.
- Not for administration as prophylactic for patients undergoing hip fracture, hip replacement, or knee replacement surgery and abdominal surgery.

Switching between anticoagulant regimens

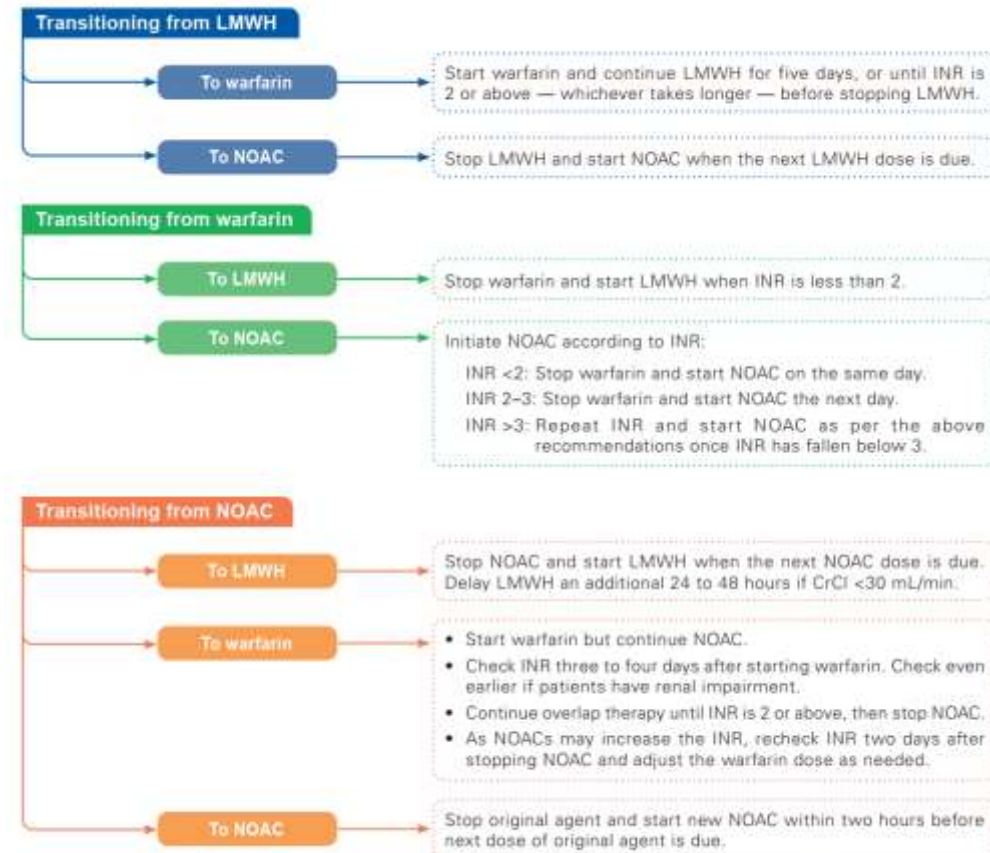


Figure 36-4: Switching between anticoagulants. Source: Agency for Care Effectiveness (ACE) (ace-hta.gov.sg).

Thrombolytics

The history of thrombolytic therapy began in 1933, when it was discovered that filtrates of broth cultures of certain streptococcal strains (beta-hemolytic streptococci) could dissolve a fibrin clot. In 1958, streptokinase was first used in patients with AMI. Streptokinase infusion initially yielded conflicting results until the GISSI trial in 1986, which validated streptokinase as an effective therapy and established a fixed protocol for its use in AMI. The fibrinolytic potential of human urine was first described in 1947, and the active molecule was named urokinase (produced in renal parenchymal cells). Tissue plasminogen activator (tPA) is a naturally occurring fibrinolytic agent found in vascular endothelial cells and is involved in the balance between thrombolysis and thrombogenesis.

Mechanism of action:

The thrombolytic agents are serine proteases that work by converting plasminogen to the natural fibrinolytic agent plasmin. Plasmin lyses clots by breaking down the fibrinogen and fibrin contained in a clot.

Classification:

Fibrinolytic agents (plasminogen activators), are divided into the following two categories:

- **Fibrin-specific agents:** Alteplase (recombinant tissue plasminogen activator [tPA]), Reteplase (recombinant plasminogen activator [r-PA]), and Tenecteplase. They produce limited plasminogen conversion in the absence of fibrin.
- **Non-fibrin-specific agents** (e.g, streptokinase) catalyze systemic fibrinolysis.

Table 36-24: Characteristics of thrombolytic medications:

| | Streptokinase | Urokinase | Alteplase | Reteplase | Tenecteplase |
|--|---------------|-----------|-----------|-----------|--------------|
|--|---------------|-----------|-----------|-----------|--------------|

| | | | | | |
|--------------------------|--|--------------------------------|--|--|--|
| Cell of origin | <i>Enzyme from (β-hemolytic strept)</i> | <i>Renal parenchymal cells</i> | <i>vascular endothelial cells</i> | <i>t-PA enz produced in E. coli via recombinant DNA technology</i> | <i>Genetically modified tPA via recombinant DNA technology</i> |
| Site of action | <i>Circulating plasminogen</i> | <i>Systemic plasminogen</i> | <i>Plasminogen at the site of clot</i> | | |
| Half life | - 85%: 20 min. - 15%: 80 min. | 8-20 min. | 5 min. | 11-19 min. | 17-21 min. |
| Clearance | <i>Hepatic</i> | <i>Hepatic</i> | <i>Hepatic</i> | <i>Renal and hepatic</i> | <i>Hepatic</i> |
| Allergic reaction | <i>5-15% allergic 0.1% anaphylaxis</i> | <i>Few allergic reactions</i> | <i>Rare</i> | <i>Rare</i> | <i>Rare</i> |

Indications:

- Thrombolytic therapy is indicated in patients with evidence of STEMI or presumably new LBBB presenting within 12 hours of the onset of symptoms if there are no contraindications to fibrinolysis.
- Acute massive PE (i.e, those at the highest risk of immediate death) and those with submassive PE with RV strain (abnormal echo or biomarkers) are eligible for fibrinolytic therapy if no contraindications are present.
- In selected patients with extensive acute proximal DVT (e.g, those with iliofemoral DVT, upper-extremity DVT, symptoms of < 14 days' duration, good functional status, or a life expectancy exceeding 1 year) whose bleeding risk is low, catheter-directed thrombolysis may be used.
- Thrombolytic Therapy for Blocked Catheters: Thrombolytic therapy has reopened occluded catheters in 85-90% of episodes, and removal of the catheter is not usually required.
- Patients who present within 4.5 hr of stroke symptom onset, should be treated with alteplase unless contraindications exist.

Doses:

| Table 36-25: Doses of thrombolytic regimens: | | |
|--|--|---|
| Molecule | Dose in STEMI | Dose in PE |
| Alteplase | 15 mg I.V bolus 0.75 mg/kg I.V over 30 min. (up to 50 mg) then 0.5 mg/kg over 60 min. (up to 35 mg) | 100 mg over 2 h 0.6 mg/kg over 15 min (max dose 50 mg) ⁽¹⁾ |
| Reteplase | 10 units + 10 units bolus given 30 min apart | Not approved by FDA for any indications except AMI |
| Tenecteplase | Single I.V bolus: - If BW < 60 kg: 30 mg (6000 IU) - If BW 60:70 kg: 35 mg (7000 IU) - If BW 70:80 kg: 40 mg (8000 IU) - If BW 80:90 kg: 45 mg (9000 IU) - If BW ≥ 90 kg: 50 mg (10000 IU) It is recommended to half the dose in patients ≥ 75 years of age. | |
| Streptokinase | 1.5 million units over 30-60 min I.V | 250.000 IU as a loading dose over 30 min, followed by 100.000 IU/h over 12-24 h Accelerated regimen: 1.5 million IU over 2 h |
| Urokinase | | 4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12-24 h Accelerated regimen: 3 million IU over 2 h |

(1) This is the accelerated regimen for rtPA in PE; it is not officially approved, but it is sometimes used in extreme haemodynamic instability.

Adverse effects:

- Hemorrhage: The most feared complication of fibrinolysis is intracranial hemorrhage (ICH), but serious hemorrhagic complications can occur from bleeding at any site in the body.
- Allergic reactions
- Embolism
- Stroke
- Reperfusion arrhythmias

Contraindications:

Table 36-26: Contraindications to fibrinolytic therapy ⁽¹⁾:

Absolute:

- Previous intracranial hemorrhage or stroke of unknown origin at anytime.
- Ischemic stroke in the preceding 6 months
- Central nervous system damage or neoplasm or arteriovenous malformation.
- Recent major trauma/surgery/head injury (within the preceding month)
- Gastrointestinal bleeding within the past month
- Known bleeding disorder (excluding menses)
- Aortic dissection
- Non-compressible punctures in the past 24 hours (e.g liver biopsy, lumbar puncture).

Relative:

- Transient ischemic attack in the preceding 6 months
- Oral anticoagulant therapy

(1) Specific contraindication to streptokinase is previous treatment with streptokinase or anistreplase.

- Pregnancy or within 1 week postpartum
- Refractory hypertension (SBP>180 mmHg and/or DBP>110 mmHg)
- Advanced Liver disease
- Infective Endocarditis
- Advanced Peptic ulcer
- Prolonged or traumatic resuscitation

Cautions:

- Reconstitute no more than 8 hr before use (does not contains antibacterial preservatives).
- Slight foaming is not unusual; let stand undisturbed for several minutes to allow large bubbles to dissipate.
- Avoid excessive agitation during dilution; mix by gently swirling and/or slow inversion.

Antiarrhythmic drugs

Classification of Antiarrhythmic drugs:

The original Vaughan Williams classification with four classes now incorporates ionic mechanisms and receptors as the basis of the more complex Sicilian Gambit system for antiarrhythmic drug classification

Table 36-27: Classification of Antiarrhythmic drug:

| Channel effects | Repolarization time | Drug examples |
|--|---------------------|--|
| Class I: divided according to their effect on action potential duration into: | | |
| Class IA: Na ⁺ block effect (++) | Prolongs | Quinidine, Disopyramide, Procainamide, Ajmaline |
| Class IB: Na ⁺ block effect (+) | Shortens | Lidocaine, Phenytoin, Mexiletine |
| Class IC: Na ⁺ block effect (+++) | Unchanged | Flecainide, Propafenone |
| Class ID: Na ⁺ block effect (+) | Prolongs | Ranolazine |
| Class II: | | |
| β-Adrenergic block I _f (pacemaker current); indirect Ca ⁺⁺ channel block | Unchanged | β-blockers (excluding sotalol that also has class III effects) |
| Class III: | | |
| Repolarizing K ⁺ currents | Markedly Prolongs | Amiodarone, Sotalol ^(1) , Dronedarone ^(2) , Ibutilide, Dofetilide, Vernakalant |
| Class IV: | | |

- (1) Sotalol is an oral class III AAD with a non-selective β-blocker effect. The β-blocker effect starts at low doses and is already half-maximal at 80 mg/day, while the class III effect starts at doses of 160 mg/day.
- (2) Dronedarone is a drug similar to amiodarone without the iodine moiety. It lacks the pulmonary and thyroid toxicity of amiodarone, affects QTc less than amiodarone, and has a shorter half-life (1-2 days compared to 2 months). Dronedarone has numerous drug interactions. It interacts with digoxin, diltiazem, and the NOACs, but not with warfarin.

| | | |
|--|-----------|----------------------|
| AV nodal Ca^{2+} block | Unchanged | Verapamil, Diltiazem |
| Class V: | | |
| K^+ channel opener (hyperpolarization) | Unchanged | Adenosine |
| Unclassified: Ivabradine | | |

Drugs Affecting the Cardiac Action Potential

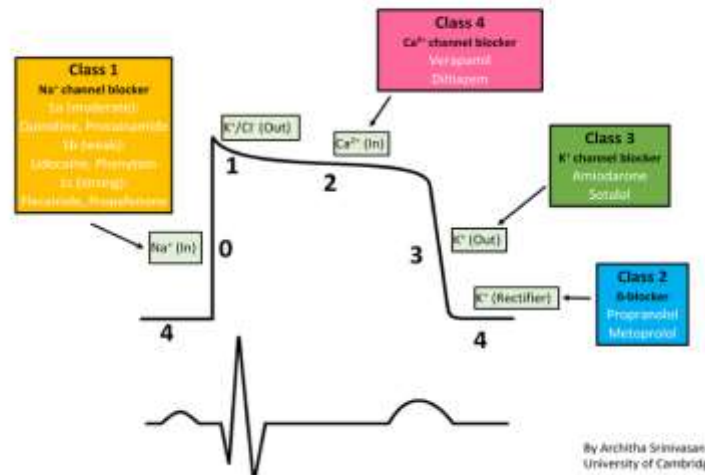


Figure 36-5: Drugs affecting the cardiac action potential. The sharp rise in voltage ("0") corresponds to the influx of sodium ions, whereas the two decays ("1" and "3", respectively) correspond to the sodium-channel inactivation and the repolarizing efflux of potassium ions. The characteristic plateau ("2") results from the opening of voltage-sensitive calcium channels.

General mechanism of action of antiarrhythmic agents:

Antiarrhythmic agents act either by slowing the conduction across a reentry loop (particularly class I agents), or by increasing the refractory period (particularly class III agents):

- **Slowing the conduction** is effective in suppressing the arrhythmia only when it creates an almost complete block across the reentry, allowing supraventricular activity to take over.

Conversely, slowing the conduction without producing a block or lengthening the refractory period may, in fact, be arrhythmogenic by itself, as the myocardium becomes more frequently “free” from the refractory period and thus excitable. This increased excitable gap allows the arrhythmia to be sustained. *Therefore, classes Ia and Ic agents should not be used in patients prone to ventricular arrhythmias (low EF, CAD).*

- **Increasing the refractory period** halts reentry, as the propagating wavefront abuts an area that is refractory. Increasing the refractory period occurs through prolonging the repolarization; *prolonging the repolarization* often exaggerates the *dispersion of repolarization*, which can initiate reentry cycles.

A prolonged repolarization may also trigger early afterdepolarizations. *This proarrhythmic effect is seen with class III drugs, but less so with amiodarone, since the latter prolongs repolarization without exaggerating the dispersion of repolarization.*

N.B:

- Proarrhythmia should be considered whenever a patient on antiarrhythmic drugs presents with a new arrhythmia or even worsening of a pre-existing arrhythmia.
- **Class I drugs:**
 - All class I drugs have a *negative inotropic effect*.
 - All class I drugs are preferably avoided in patients with a baseline QRS > 120 ms, as they further impair infranodal conduction; they should be discontinued if QRS prolongs > 25% after initiation of therapy. A stress test may be performed a week after therapy initiation to unveil QRS prolongation with exercise/tachycardia.
 - Class I agents are ineffective in cardioverting atrial flutter and may actually allow it to sustain, as they slow the conduction across the large macroreentry, widening its excitable gap.

- Class Ia and Ic agents slow the reentrant circuits, thereby reducing the rate of the fibrillatory AF impulses. The non-conducted atrial impulses partially penetrate the AV node and make it partially refractory to subsequent impulses (concealed conduction); thus, a reduction in the rate of atrial impulses allows more impulses to conduct through the AV node, which paradoxically increases the ventricular rate.
- Class I agents and amiodarone increase defibrillation threshold, (i.e., increase the energy requirement for defibrillation of VT/VF). Class I agents also increase pacing threshold, which may lead to a loss of capture.
- Class III drugs prolong QT and are associated with a dose-dependent risk of TdP (~2% with sotalol or dofetilide, less so with amiodarone). They should be avoided in patients with QTc > 460 ms at baseline (or >500 ms when QRS > 120 ms), or if QTc increases by > 15% or to > 500ms with therapy.

Table 36-28: Quick reference for common antiarrhythmic drugs:

| Agent | Dose | Pharmacokinetics and metabolism | Side effects and contraindications | Interactions and precautions |
|------------------------------|---|---|---|--|
| Lidocaine (class IB) | IV: 75–200 mg; then 2–4 mg/min for 24–30 h. (No oral use) | <i>Effect of single bolus lasts only few min, then T_{1/2} approximately 2 h.</i> <i>Rapid hepatic metabolism.</i> Level: 1.4–5 µg/mL; toxic >9 mcg/mL. | <i>Reduce dose by half if liver blood flow low (shock, β-blockade, cirrhosis, cimetidine, severe HF).</i> <i>High dose CNS effects</i> | <i>β-blockers decrease hepatic blood flow and increase blood levels.</i> <i>Cimetidine (decreased hepatic metabolism of lidocaine).</i> |
| Mexiletine (class IB) | IV: 100–250 mg at 12.5 mg/min, then 2 mg/kg/h for 3.5h, then 0.5 mg/kg/h. PO: 100–400 mg TDS; loading dose 400 mg. | T_{1/2} =10–17 h. Level =1–2 µg/mL. <i>Hepatic metabolism, inactive metabolites.</i> | <i>CNS, GI side effects.</i> <i>Bradycardia, hypotension esp. during cotherapy.</i> | <i>Enzyme inducers; disopyramide and β-blockade; increases the theophylline levels.</i> |
| Phenytoin (class IB) | IV: 10–15 mg/kg over 1 h. PO: 1 g; 500 mg for 2 days; then 400–600 mg daily. | T_{1/2} =24 h. <i>Level</i> 10–18 µg/mL. <i>Hepatic metabolism.</i> <i>Hepatic or renal disease requires reduced doses.</i> | <i>Hypotension, vertigo, dysarthria, lethargy, gingivitis, macrocytic anemia, lupus, pulmonary infiltrates.</i> | <i>Hepatic enzyme inducers</i> |
| Flecainide (class IC) | IV: 1–2 mg/kg over 10 min, then 0.15–0.25 | T_{1/2} =13–19 h. <i>Hepatic 2/3; 1/3 renal excretion unchanged.</i> | <i>QRS prolongation.</i> <i>Proarrhythmia.</i> <i>Depressed LV function.</i> | <i>Many, especially added inhibition of conduction and nodal tissue.</i> |

| | | | | |
|----------------------------------|--|--|---|---|
| | mg/kg/h. PO: 50–400 mg BID. Hospitalize. | Keep trough level below 1 $\mu\text{g/mL}$. | CNS side effects. \uparrow incidence of death postinfarct. | |
| Propafenone (class IC) | IV: 2 mg/kg then 2mg/min. PO: 150–300 mg TDS. | T_{1/2} =variable 2–10 h, up to 32 h in nonmetabolizers. Level =0.2–3 $\mu\text{g/mL}$. Variable hepatic metabolism (P-450 deficiency slows). | QRS prolongation. Modest negative inotropic effect. GI side effects. Proarrhythmia. | Digoxin level increased. Hepatic inducers. |
| Ibutilide (class III) | IV infusion: 1 mg over 10 min, (If <60 kg: 0.1 mg/kg). If needed, repeat after 10 min. | Initial distribution T_{1/2} =1.5 min. Elimination T _{1/2} averages 6 h (range 2–12 h). Efficacy is usually within 40 min. | Nausea, headache, hypotension, bundle branch block, AV block, bradycardia, tdp, sustained VT, ventricular extrasystoles. Avoid concurrent class I or III drugs. Care with amiodarone or sotalol. C/I: previous tdp, decompensated heart failure. | Interactions with Class IA and other class III antiarrhythmic drugs that prolong the QT interval (e.g. antipsychotics, antidepressants, macrolide antibiotics, and some antihistamines). Check QT. Correct hypokalemia and hypomagnesemia. |
| Dofetilide (class III) | Dose: 250 μg BID, max. | Oral peak plasma concentration in 2.5 hrs and steady state within 48 h. | Tdp in 3% of patients which can be reduced by ensuring normal serum K, avoiding | Increased blood levels with ketoconazole, verapamil, cimetidine, or inhibitors of |

| | | | | |
|-------------------------------|--|--|--|---|
| | <p>500 µg BID if normal renal and cardiac function.</p> <p>If LV dysfunction, 250 µg BID.</p> <p>Check QT 2–3 h after dose, if QTc is 15% or > 500 ms, reduce dose.</p> <p>If QTc >500 ms, stop.</p> | <p>50% excreted by kidneys unchanged.</p> | <p>dofetilide or reduce the dose if abnormal renal function, bradycardia, or base-line QT".</p> <p>Avoid other drugs increasing QT.</p> <p>C/I: previous Tdp, cr.cl. <20mL/min.</p> | <p>cytochrome CYP3A4, including macrolide antibiotics, protease inhibitors such as ritonavir.</p> <p>Other precautions as previously.</p> |
| Sotalol (class III) | <p>80–640 mg daily, occasionally higher in two divided doses.</p> | <p>T_{1/2}=12 h. Not metabolized.</p> <p>Hydrophilic.</p> <p>Renal loss.</p> | <p>Myocardial depression, sinus bradycardia, AV block.</p> <p>Tdp if hypokalemic.</p> | <p>Added risk of torsades with IA agents or diuretics. Decrease dose in renal failure.</p> |
| Amiodarone (class III) | <p>PO:</p> <p>Loading: 600–1200 mg OD;</p> <p>Maintenance: 50–400mg/d</p> <p>IV: 150 mg over 10 min, then 360 mg over 6 h, then 540 mg over remaining 24h, then 0.5 mg/min.</p> | <p>T_{1/2}=25–110 days.</p> <p>Level=1–2.5 µg/mL.</p> <p>Hepatic metabolism.</p> <p>Lipid soluble with extensive distribution in body.</p> <p>Excretion by skin, biliary tract, lacrimal glands.</p> | <p>Complex dose dependent side effects including pulmonary fibrosis.</p> <p>QT prolongation. Tdp uncommon.</p> | <p>Class IA agents predispose to Tdp.</p> <p>β-blockers predispose to nodal depression, yet give better therapeutic effects.</p> |

Amiodarone

Mechanism of action:

- Class III antiarrhythmic agent, which affects sodium, potassium, and calcium channels; markedly prolongs action potential and repolarization; decreases AV conduction and sinus node function.
- *Amiodarone* mainly has class III and sympatholytic effects, but also class I and vasodilator effects.
Acutely, amiodarone mostly causes a sympatholytic and class I effect; class III effect occurs later. Thus, the effect of amiodarone on ventricular repolarization is slow, with QT prolongation appearing at 4–10 days of therapy. Also, in AF, the early effect is rate slowing (the effect on AF conversion is late).

Indications:

- Stable Monomorphic or Polymorphic Ventricular Tachycardia:
 - IV: 150 mg IV bolus in 10 minutes; may repeat q10min as necessary, 360 mg over next 6 hr (1 mg/min), THEN 540 mg over remaining 18 hr (0.5 mg/min); not to exceed 2.2 g/24hr.
For breakthrough episodes of VF or hemodynamically unstable VT, repeat the initial load.
 - PO: Load: 800-1600 mg PO qDay for 1-3 weeks until response; once adequate arrhythmia control achieved, reduce dose to 600-800 mg/day for 1 mo; THEN reduce to maintenance dose. Maintenance: 400 mg PO qDay.
- ACLS, Pulseless VF/VT:
 - 300 mg IV or intraosseous push after dose epinephrine if no initial response to defibrillation
 - May follow initial dose with 150 mg IV q3-5min

Adverse effects:

- Hypotension (16%): is the most common adverse reaction; in some cases, hypotension may be refractory and result in a fatal outcome.

- **Thyroid toxicity:** Around 1 in 6 patients taking amiodarone develop thyroid dysfunction.
- Amiodarone contains iodine and inhibits the T4-to-T3 deiodinase. This leads to increased free T4, reduced T3, and increased TSH early on (first 3–6 months). This is a benign, normal phenomenon. Amiodarone has the following effects on the thyroid system:
- *Amiodarone-induced hypothyroidism:* The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect ⁽¹⁾. Amiodarone may be continued if this is desirable.

Amiodarone-induced thyrotoxicosis: may be divided into two types:

| Table 36-29: Amiodarone-induced thyrotoxicosis: | | |
|---|---|--|
| | AIT type 1 | AIT type 2 |
| Pathophysiology | Excess iodine-induced thyroid hormone synthesis | Amiodarone-related destructive thyroiditis |
| Goitre | Present | Absent |
| Management | Carbimazole <u>or</u> K perchlorate | Steroids for 1 month with subsequent taper |

- If hypothyroidism is present at baseline or develops with therapy, amiodarone may still be used as long as levothyroxine therapy is provided, and the thyroid function is closely monitored.
- If hyperthyroidism develops, amiodarone should often be stopped. Due to the long half-life of amiodarone, the thyroid function will not improve for a few months. That is why it is acceptable to continue amiodarone for a few more days if necessary (e.g., VT).
- **Lung toxicity:**
- It may develop acutely in days (rare), subacutely, or chronically. Usually presents as hypersensitivity pneumonitis or interstitial/alveolar pneumonitis (10-17% incidence with 400 mg/day). Fatal in ~10% of cases.

(1) an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide.

- Amiodarone lung toxicity often simulates pulmonary edema/heart failure progression. Amiodarone toxicity should therefore be sought in any patient receiving amiodarone whose pulmonary function is not improving with diuresis and/or antibiotic therapy.
- The earliest and most sensitive abnormality is a reduction of diffusion capacity (DLCO). Therefore, it is important to perform a lung function study before initiation of therapy, then be repeated every year.
- No diagnostic test is specific for amiodarone lung toxicity. Mononuclear cells on bronchoalveolar lavage are consistent with amiodarone therapy and do not necessarily imply toxicity. The clinical context, a refractory pulmonary process, and DLCO are most useful for diagnosis.
- The lung toxicity is reversible only if diagnosed early, and sometimes improves with steroids.
- **Proarrhythmic effect:**
 - Like other antiarrhythmics, can exacerbate the arrhythmia (eg, by making the arrhythmia less well tolerated or more difficult to reverse).
 - 2-5% incidence; includes significant heart block or sinus bradycardia.
 - Effects are prolonged when they occur because of long drug half-life.
 - Neuropathy, ataxia (dose-dependent).
 - Blue skin discoloration.
 - Liver injury: increased liver AST or ALT levels (3-20%; as high as 40-50% in some studies)
 - Sleep disturbances (3-40%)
 - Corneal microdeposits appear in majority of adults treated; usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision up to 10% of patients; corneal microdeposits are reversible upon reduction or termination of treatment; asymptomatic microdeposits alone are not reason to reduce dose or discontinue treatment.
 - Infusion site phlebitis has occurred in patients receiving intravenous amiodarone; intravenous amiodarone concentrations greater than 3 mg/mL associated with a high incidence of peripheral vein phlebitis.

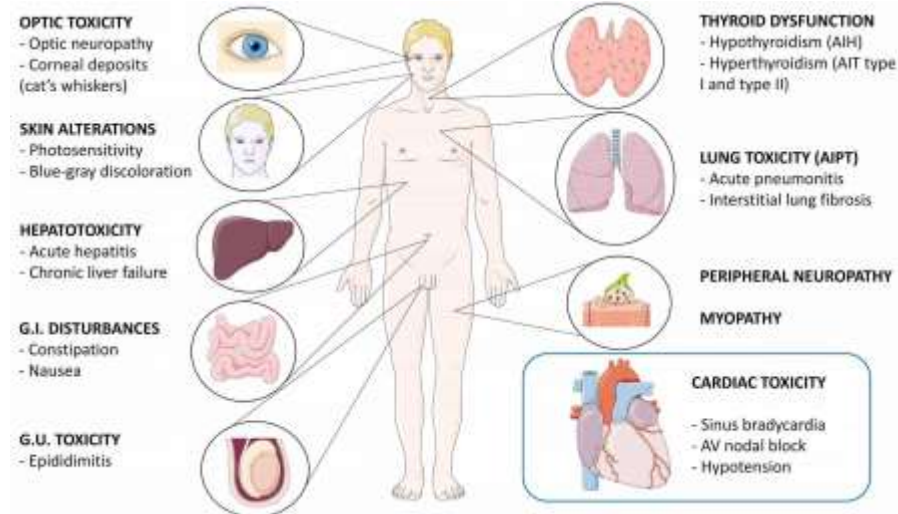


Figure 36-6: Amiodarone side effects. Source: Pannone L, D'Angelo G, Gulletta S, et al. Amiodarone in ventricular arrhythmias: still a valuable resource?. Reviews in Cardiovascular Medicine. 2021 Dec 22;22(4):1383-92.

Contraindications:

- Hypersensitivity.
- Severe sinus node dysfunction, 2°/3° AV block or bradycardia causing syncope (except with functioning artificial pacemaker), cardiogenic shock.
- Avoid during breastfeeding.

Cautions:

- Avoid excessive exposure to sunlight; may cause photosensitivity.
- Correct hypokalemia, hypomagnesemia or hypocalcemia before initiating treatment as these disorders can exaggerate the degree of QTc prolongation and increase the potential for TdP.

- Causes increased INR; use caution when initiating therapy in patients treated with warfarin.
- Monitor thyroid function prior to treatment and periodically thereafter, particularly in elderly patients.

Drug interactions:

- Serious symptomatic bradycardia when co-administered with ledipasvir/sofosbuvir or with sofosbuvir with simeprevir; some requiring pacemaker insertion.
- Concomitant use of drugs with depressant effects on sinus and AV node (e.g., digoxin, b-blockers, verapamil, diltiazem, ivabradine, clonidine) can potentiate effects of amiodarone, resulting in bradyarrhythmia.
- Amiodarone may raise the levels of digoxin and warfarin (the “A–D” and “A–W” interaction). These drugs should routinely be reduced by one-half, and levels followed closely when amiodarone is started.
- Amiodarone increases the levels of the NOACs, particularly rivaroxaban.

Adenosine

Mechanism of action:

- **Paroxysmal Supraventricular Tachycardia (PSVT):** agonist of the A1 receptor in the atrioventricular node, which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux → Slow conduction through AV node and interrupts AV reentry pathways.
- **Stress testing:** A2A adenosine receptor agonist; activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow.

Adenosine effects:

- Adenosine activates an outward potassium current (IK, ADO), which leads to hyperpolarization of the *sinus node and AV node*, causing them to block conduction, thus terminating AVNRT, AVRT, and SNRT.
- Adenosine antagonizes the cardiac effect of catecholamines by inhibiting adenylyl cyclase, the enzyme that generates cAMP; thus, adenosine may terminate *catecholamine-triggered arrhythmias*.
- Automatic atrial tachycardia may be transiently suppressed by the hyperpolarizing effect of adenosine, but owing to its incessant nature the tachycardia quickly resumes.

Indications & clinical evidence:

- **PSVT:** Indicated for conversion to sinus rhythm of paroxysmal supraventricular tachycardia, including that associated with accessory bypass tracts (e.g WPW Syndrome)
Adenocard: 6 mg IVP over 1-3 seconds (maybe given IO) followed by rapid flush with 20 mL NS, if no conversion within 1-2 minutes gives 12 mg IVP, repeat a second time if necessary (30 mg total)
- **Stress Testing (Diagnostic):** Indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. Adenoscan: 140 mcg/kg/min IV infusion for 6 min.

Adverse effects:

- Chest pain
- Transient flushing (18%)
- Dyspnea (12%)
- Can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW).

Contraindications:

- Sinus node disease or AV block (except those on pacemakers)
- Adenoscan: Contraindicated in bronchoconstrictive or bronchospastic lung disease (eg, asthma)

Cautions:

- Adenosine should ideally be infused via a large-calibre cannula due to its short half-life (8-10 seconds).
- New-onset or recurrence of convulsive seizures; aminophylline may increase risk of seizures associated with adenosine; so, it is not recommended in patients who experience seizures with adenosine.

Drug interactions:

The effects of adenosine are enhanced by dipyridamole (antiplatelet agent) and blocked by theophyllines.

Ivabradine

Ivabradine was first introduced as an anti-anginal medicine by the European Medicines Agency (EMA) in 2005 and then as a heart failure medicine in 2012. On April 2015, it was approved by the FDA for the treatment of stable angina and systolic heart failure (HF).

Mechanism of action:

Ivabradine is a specific pure bradycardiac agent targeting HCN channels (hyperpolarization-activated inward current). These channels generate an inward diastolic Na⁺ and K⁺ current initiating spontaneous pacemaker activity, which is called *I_f* (known as the funny channel ⁽¹⁾).

Treatment with ivabradine causes a dose-dependent reduction in heart rate by selective and specific inhibition of the cardiac pacemaker *I_f* current that controls spontaneous depolarization in the sinus node and hence regulates heart rate. The usual effect is a 10 bpm reduction in heart rate whether at rest or during exercise. The fall in heart rate leads to a reduction in cardiac workload and myocardial oxygen consumption.

Indications and Clinical evidence:

Table 36-30: Clinical trials of ivabradine:

| Trial (date) | Summary |
|--|---|
| Chronic stable angina (in patients unable to tolerate, or with a contraindication to, the use of B-blockers) | |
| Ivabradine was approved by the European Medicines Agency (EMA) for therapy of chronic stable angina in patients intolerant to or inadequately controlled by b-blockers and whose heart rate exceeded 60 b.p.m. (in sinus rhythm). Ivabradine is thus an effective anti-anginal agent, alone or in combination with b-blockers. | |
| BEAUTIFUL (2008) | <i>In patients who had CAD and LVEF < 40%, reduction in heart rate with ivabradine does not improve cardiac outcomes in all patients with SCAD and LV systolic dysfunction, but could reduce the incidence of CAD outcomes in a subgroup of patients who have heart rates of ≥ 70 bpm.</i> |
| Heart Failure: | |

(1) These channels are called 'funny' as such a current was unexpected by the scientist who discovered it.

Indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LVEF $\leq 35\%$, who are in sinus rhythm with resting heart rate ≥ 70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

| | |
|-------------------------|---|
| SHIFT (2010) | <i>In patients with symptomatic heart failure and LVEF $\leq 35\%$ in sinus rhythm with heart rate ≥ 70 b.p.m, ivabradine resulted in 5% absolute reduction in HF mortality or hospitalization at 2 years.</i> |
|-------------------------|---|

Adverse effects:

- *Visual symptoms*: most commonly reported adverse effect. Luminous phenomena occurred in 15% of patients, and therefore new patients should be warned about this potential transient side-effect. The possible occurrence of such luminous phenomena should be taken into account when driving especially at night or using machines in situations where sudden variations in light intensity may occur.
- *Cardiac conduction effects*: bradycardia, 1st-degree AV block, PVCs can occur during therapy (10%)
- *Hypertension or increased blood pressure* (8.9%)
- *Atrial fibrillation* (8.3%)
- *Heart block*.
- *Headache*: generally during the early treatment phase
- *Dizziness*: possibly related to bradycardia
- *GI disturbances*: nausea, vomiting, diarrhoea.

Contraindications:

- Acute decompensated heart failure.
- Clinically significant hypotension.
- Sick sinus syndrome, SA block, or third-degree AV block (unless a functioning demand pacemaker is present).

- Clinically significant bradycardia
- Severe hepatic impairment.
- Severe renal dysfunction (no evidence on safety or pharmacokinetics for CrCl < 15 mL/min).
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker)
- Concomitant use of strong CYP3A4 inhibitors.
- Pregnancy or breastfeeding.

Cautions:

- Increases the risk of AF; regularly monitor cardiac rhythm and discontinue drug if AF develops
- May cause fetal toxicity when administered to a pregnant woman; inform women of childbearing potential to use effective contraception
- Concurrent heart-rate lowering agents, post-CVA, retinitis pigmentosa, hypotension (avoid if BP < 90/50 mmHg), hepatic insufficiency (avoid if severe), severe renal insufficiency (CrCl < 15 mL/min).
- Chronic retinal diseases, including retinitis pigmentosa. Visual phenomena are usually transient and disappear during the first few months of ivabradine treatment and are not associated with serious retinal dysfunction. However, if they result in patient's discomfort, discontinuation of ivabradine should be considered.
- In case of lactose or galactose intolerance (component of the ivabradine tablet), if symptoms occur, there may be a need to stop the drug.

Monitoring:

- Obtain baseline BP and pulse before initiation and after each change in dose.
- In the absence of adverse effects, review within 4 weeks and consider increasing the dose if required for better symptom control.

Drug interactions:

- Coadministration of ivabradine with *strong CYP3A4 inhibitors* (e.g., clarithromycin, ketoconazole, Voriconazole, quinidine) is contraindicated as they will increase the level or effect of ivabradine.
- Coadministration of *verapamil or diltiazem* with ivabradine increases ivabradine systemic exposure and should be avoided.
- Concomitant use with negative chronotropes (eg, digoxin, amiodarone, beta-blockers) may increase the risk of bradycardia; monitor heart rate in patients taking ivabradine with other negative chronotropes.

Angiotensin-converting enzyme inhibitors (ACEIs)

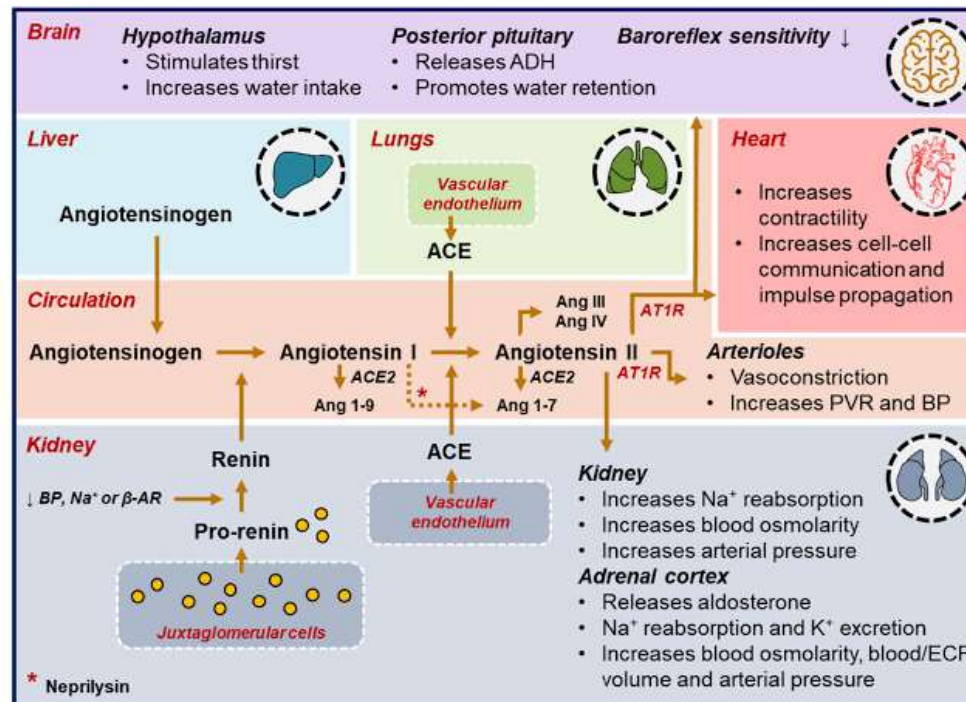


Figure 36-7: The renin-angiotensin-aldosterone activation cascade. Source: Sutanto H, Dobrev D, Heijman J. Angiotensin receptor-neprilysin inhibitor (ARNI) and cardiac arrhythmias. International journal of molecular sciences. 2021 Aug 20;22(16):8994.

Mechanism of action:

- ACEIs competitively inhibit:

- Angiotensin converting enzyme. ACE is a non-specific enzyme involved in the metabolism of many small peptides, including the conversion of angiotensin I into angiotensin II. Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, resulting in sodium and water retention.
 - Kininase, an enzyme that catalyses the degradation of bradykinin and other potent vasodilator peptides.
 - Aldosterone and vasopressin secretion and decrease sympathetic nerve activity as well as the trophic effects of angiotensin-II.
 - ACE-Is lead to vasodilatation and prevent the buildup of fluid that would result from aldosterone release.
- Since the mechanism of action of ACE-I is the same, their effects are attributed to the class as a whole. In fact, all currently available ACE-I can be considered equally effective at lowering blood pressure. Therefore, the choice and dose of the ACE-I should be based on the results of clinical trials where the benefit has been demonstrated.

Indications & clinical evidence:

| Table 36-31: Clinical trials of ACE-Is: | |
|--|--|
| Trial (date) | Summary |
| Heart failure: | |
| ACE-I are indicated as first-line therapy in patients with a reduced LV systolic function (LVEF <40%), with or without heart failure symptoms, in absence of contraindications. The clinical benefit includes a reduction in mortality, rehospitalization and progression of heart failure. ACE-I should not be titrated based on symptomatic improvement alone but uptitrated to the dosages shown to be effective in the large, controlled trials in heart failure and LV dysfunction. | |
| CONSENSUS (1987) | <i>In patients with NYHA class IV HFrEF, enalapril improves survival when added to standard therapy.</i> |
| SOLVD (1991) | <i>In patients with HFrEF, enalapril reduces 4-year mortality by 16% and reduces HF hospitalizations when added to conventional therapy.</i> |

| | |
|---|---|
| TRACE (1995) | <i>In patients with MI, long-term treatment with trandolapril in patients with reduced LV function soon after MI significantly reduced the risk of overall mortality, CV mortality, sudden death, and the development of severe heart failure.</i> |
| ATLAS (1999) | <i>In patients with NYHA classes II-IV CHF and LVEF < 30%, high dose of lisinopril reduced CV mortality by 10%, combined all-cause mortality or HF hospitalization rate by 15%.</i> |
| Acute myocardial infarction: | |
| Oral ACE-I are beneficial in AMI patients when administered within 36 h of the event, especially in the presence of anterior infarcts, impaired ejection fraction or mild-moderate heart failure. Following AMI, patients with clinical heart failure or asymptomatic LV dysfunction should be treated long term with ACE-I, as well as patients at high risk or with diabetes. | |
| GISSI-3 (1995) | <i>In patients presented with acute MI, lisinopril when given within 24 hours of acute MI reduced mortality by 11% at 6 weeks. No benefit for transdermal glyceryl trinitrate.</i> |
| ISIS-4 (1995) | <i>In patients after the onset of suspected AMI, captopril showed a reduction in mortality at 5 weeks with the largest advantage in high-risk individuals. There was no mortality benefit for isosorbide mononitrate or IV magnesium.</i> |
| AIRE (1997) | <i>In patients with clinical or radiological evidence of heart failure within 2-9 days of MI, ramipril reduces mortality and progression to resistant heart failure. Retarding the progression of heart failure appears to be a major factor contributing to the reduction in mortality both by reducing circulatory failure and by reducing sudden death.</i> |
| Hypertension: | |
| ANBP-2 (1997) | <i>In hypertensive patients, ACE-I (enalapril) and diuretic (hydrochlorothiazide) showed similar blood pressure reduction, but after a follow-up period of 4.1 years, the cumulative rate of death and CV events was lower in the group receiving ACE-I (56.1 vs 59.8 per 1000 patient-years), mainly due to a decrease in MI, while the incidence of stroke was similar.</i> |

| | |
|---|---|
| ABCD (1998) | <i>As a first-line antihypertensive agent in terms of the prevention and progression of complications of diabetes throughout five years of follow-up, Nisoldipine was associated with a higher incidence of fatal and non-fatal MI than enalapril, but the number of infarct episodes was simply too low to reach any conclusion. Mortality was similar in both groups.</i> |
| CAPPP (1999) | <i>In patients with hypertension, captopril and conventional treatment (diuretic and B-blockers) did not differ in efficacy in preventing CV morbidity (a combination of MI, stroke and CV mortality), but the incidence of stroke was higher in the captopril group. Conversely, the incidence of diabetes during the follow-up was lower in the captopril group.</i> |
| PROGRESS (2001) | <i>In hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack, perindopril, with the addition of indapamide at the discretion of treating physicians reduced the incidence of stroke (10% vs. 14%) and also the risk of total major vascular events. The reduction of stroke was similar in hypertensives and normotensives. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions (43%) than did single drug-therapy with perindopril alone. Single-drug therapy produced a clinically relevant reduction in the risk of stroke.</i> |
| ALLHAT (2002) | <i>In hypertensive patients with at least one other cardiovascular risk factor, lisinopril had higher 6-year rates of combined CV disease; stroke; and HF, and this brings into question use of ACE-I as first line therapy in hypertensive patients without high risk profile or heart failure.</i> |
| Secondary prevention and high-risk of cardiovascular disease: | |
| ACEIs have been shown to reduce the risk of CV events in patients who are at high risk of events, such as those with established atherosclerotic disease. | |
| QUIET (2001) | <i>In patients after angioplasty with normal LV function, quinapril was well tolerated in patients. Quinapril did not significantly affect the overall frequency of clinical outcomes or the progression of coronary atherosclerosis.</i> |
| SCAT (2001) | <i>Enalapril failed to reduce the severity of coronary lesions as compared with placebo.</i> |

| | |
|----------------------------|---|
| HOPE (2000) | <i>In high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other CV risk factor and who were not known to have a low EF or heart failure, ramipril significantly reduces the rates of death, MI, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.</i> |
| EUROPA (2003) | <i>In patients with stable coronary heart disease without apparent heart failure, perindopril can significantly improve outcome. Treatment with perindopril, on top of other preventive medications, should be considered in all patients with coronary heart disease.</i> |
| PEACE (2004) | <i>In patients with stable coronary artery disease and normal or slightly reduced LV function, there is no evidence that the addition of an ACE-I provides further benefit in terms of death from CV causes, MI, or coronary revascularization.</i> |
| ONTARGET (2008) | <i>Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.</i> |

Adverse effects:

- *First-dose hypotension* particularly in patients with high plasma renin activity (e.g., salt-depleted patients due to high doses of diuretics or with congestive heart failure): use a long-acting agent, avoid excessive diuresis prior to initiation. First dose may be given at night before bed to reduce the risk of hypotension and associated falls.
- *Dry cough*: occurs in around 10% of patients. It is thought to be due to increased bradykinin and/or substance P in the lungs. Cough is not dose-dependent, is more frequent among women and in Asian populations, it usually develops between 1 week and a few months of treatment. Once therapy is stopped, cough usually disappears within 3-5 days. Consider an ARB if cough recurs/persists. Cough is also a symptom of pulmonary oedema, which should be excluded when a new worsening cough develops.

- *Angioedema*: a rare but potentially life-threatening adverse effect. It may occur up to a year after starting treatment. ACE-I therapy should be stopped and specialist advice sought before re-initiation.
- *Rash*: switch ACE-I and if rash persists consider ARB.
- *Hyperkalemia* due to a decrease in aldosterone secretion is rarely found in patients with normal renal function but it is relatively common in those with congestive heart failure and in the elderly. Hyperkalemia is more frequent in patients with renal impairment, diabetes, receiving either Kp or potassium Kp-sparing diuretics, heparin or NSAIDs.
- *Acute renal failure*. ACE-I can increase blood urea nitrogen or creatinine levels. In most patients creatinine levels either will remain stable or decrease towards pretreatment values during continued treatment. Acute renal failure is more frequent in patients with volume depletion due to high doses of diuretics, hyponatremia, bilateral renal artery stenosis, stenosis of the dominant renal artery or a single kidney and renal transplant recipients.
- *Proteinuria*. ACE-I can produce proteinuria. However, pre-existing proteinuria is not a contraindication for ACEI, as they have been found to exert nephroprotective effects in renal diseases associated with proteinuria (i.e., diabetic nephropathy).
- *Teratogenic effects*. When administered during the second or third trimester of pregnancy, ACE-I can cause foetal abnormalities (i.e., oligohydramnios, pulmonary hypoplasia, foetal growth retardation, renal dysgenesis, neonatal anuria and neonatal death)

Contraindications:

- Aortic stenosis: may result in hypotension
- Angioedema (any cause): The safety of ARBs in patients developing angioedema with ACE-I is uncertain.
- Hypersensitivity to ACE-Is
- Known bilateral renal artery stenosis
- Pregnancy and breastfeeding: Although ACE-I are not contraindicated in women of reproductive age, they should be discontinued as soon as pregnancy is suspected or diagnosed.
- ACE-I, as well as other vasodilators, should also be avoided in patients with dynamic LVOT obstruction.

Cautions:

- Hypotension with SBP < 80 mmHg **or** with symptoms of low output (dizzy, obtunded, oliguric). A low SBP of 80–90 mmHg may be well tolerated in HF because it helps unload the LV; ACE-I is started slowly and the diuretic is reduced if possible.
- Elevation of creatinine of over *50% within 1–2 weeks of ACE-I/ARB initiation*. An increase in creatinine of up to 50% above baseline, or 3 mg/dL, or eGFR <25 mL/min/1.73 m², whichever is the smaller, is acceptable ⁽¹⁾. An increase in K⁺ to ≤ 5.5 mmol/L is also acceptable.
- If urea, creatinine, or K⁺ does rise excessively:
 - ☞ Consider stopping nephrotoxic drugs (e.g., NSAIDs) and other K⁺ supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic.
 - ☞ If greater rises in creatinine or K⁺ persist, the dose of the ACE-I (or ARB) should be halved and blood chemistry re-checked within 12 weeks; if there is still an unsatisfactory response, specialist advice should be sought.
 - ☞ If K⁺ rises to > 5.5 mmol/L or creatinine increases by > 100% or to > 3.5 mg/dL or eGFR <20 mL/min/1.73 m², the ACE-I (or ARB) should be stopped and specialist advice sought.
 - ☞ Bilateral renal artery stenosis may need to be ruled out.
- Patients on high-dose diuretics (i.e., furosemide > 80 mg daily)
- Breast-feeding

Monitoring:

- Obtain baseline BP and urea and electrolytes (U&Es) before initiation
- Check BP and U&Es within two weeks of initiation or change of dose, then annually.
- If potassium rises to > 6.0 mmol/L or creatinine increases by > 50% or to above 3 mg/dL (256 mmol/L) the administration of ACE-I should be stopped.

(1) In fact, In one study, patients with early worsening of renal function appeared to derive the largest benefit from ACE-I.

- ACE-I dose should only be increased if:
 - Systolic blood pressure > 90 mmHg
 - Serum creatinine increases by less than 20% (or eGFR falls by < 15%) on each dose titration
 - Potassium < 5.5 mmol/L.

Drug interactions:

- *Ciclosporin*: increases risk of hyperkalaemia
- *Diuretics*: patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - significantly increases the risk of hypotension
- *Lithium*: increases lithium levels
- *Potassium supplements*: increased risk of severe hyperkalaemia.
- *Antacids* may reduce the availability of ACE-I.
- *Non-steroidal anti-inflammatory drugs* may reduce the vasodilator effects of ACE-I.

Pharmacological notes:

- ACE-I are classified in three categories according to the group that binds the zinc atom of the ACE molecule into those containing a sulfhydryl, a carboxyl or a phosphoryl group as zinc ligand.
- The absorption is highly variable among ACE-I (25–75%) and food either has no effect or reduces the rate, but not the extent of absorption.
- Some ACE-I are pro-drugs and they remain inactive until they are converted into active metabolites by hydrolysis in the liver or in the gastrointestinal tissue.
- The peak plasma drug concentrations are reached 1–4 h after ingestion.
- Pro-drugs are more lipophilic and they have a better access to the target tissue where they are converted to the active compound.

- Most ACE-I and their metabolites are mainly excreted by the renal route, whereas fosinopril, zofenopril, trandolapril and spirapril display balanced elimination through hepatic and renal routes. Captopril is eliminated more rapidly from the body, which accounts for its brief duration of action (<6 h), whereas ramipril and tandrolapril are eliminated more slowly than other ACE-I.
- Due to diminished renal perfusion, renal excretion may be reduced, leading to elevated maximum drug plasma levels and prolonged duration of action. Thus, dose reductions are required in the presence of impaired renal function. Fosinopril, spirapril, trandolapril and zofenopril are excreted in both the urine and bile, so that their clearance is not significantly altered by renal impairment.

| Table 36-32: Pharmacological properties of various ACE-I: | | | | |
|---|-----------------------|-----------------------|---------------|---|
| Drug | Elimination half-life | Renal elimination (%) | Dose (mg) | Dose (mg) in renal failure (CrCl 10–30 ml/min) |
| Sulfhydryl-containing inhibitors: | | | | |
| Captopril | 2 | 95 | 25-100 t.i.d. | 6.25–12.5 t.i.d. |
| Benazepril | 11 | 85 | 2.5-20 b.i.d. | 2.5–10 b.i.d. |
| Zofenopril | 4.5 | 60 | 7.5-30 b.i.d. | 7.5–30 b.i.d. |
| Carboxyl-containing inhibitors: | | | | |
| Enalapril | 11 | 88 | 2.5-20 b.i.d. | 2.5–20 b.i.d. |
| Lisinopril | 12 | 70 | 2.5-10 daily | 2.5–5 daily |
| Ramipril | 8–14 | 85 | 2.5-10 daily | 1.25–5 daily |
| Perindopril | >24 | 75 | 4-8 daily | 2 daily |
| Cilazapril | 10 | 80 | 1.25-5 daily | 0.5–2.5 daily |
| Quinapril | 2–4 | 75 | 10-40 daily | 2.5–5 daily |
| Spirapril | 1.6 | 50 | 3-6 daily | 3–6 daily |

| | | | | |
|--|-------|----|-------------|-------------|
| Trandolapril | 16–24 | 15 | 1-4 daily | 0.5–1 daily |
| Phosphinyl-containing inhibitors: | | | | |
| Fosinopril | 12 | 50 | 10-40 daily | 10–40 daily |

Angiotensin receptor blockers (ARBs)

Mechanism of action:

ARBs bind to the angiotensin II receptors and therefore block the action of angiotensin II. Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, which increases sodium and water retention. ACE-Is therefore lead to vasodilatation and prevent the buildup of fluid that would result from aldosterone release. Unlike ACE-Is the ARBs do not inhibit the breakdown of bradykinin that is responsible for ACE-I-induced cough.

N.B: Not all ARBs are the same Selectivity on AT1 Receptor. Valsartan is 3 times more selective for AT1 receptors than other ARB agents.

Indications and Clinical evidence:

Table 36-33: Clinical trials of ARBs:

| Trial (date) | Summary |
|---|--|
| Heart failure: | |
| <ul style="list-style-type: none">○ ARBs are second line to ACE-I (i.e. ACE-I-intolerant patients) in all patients with any degree of left ventricular systolic function, initiated as early as possible following diagnosis○ Candesartan may also be considered in addition to ACE-I for inpatients remaining symptomatic despite optimal ACE treatment, if they are unable to tolerate spironolactone. | |
| ELITE-II (2000) | <i>Losartan compared to captopril would improve survival in patients with congestive heart failure and impaired LV systolic function.</i> |
| ValHeFT (2001) | <i>In patients with heart failure of NYHA class II-IV, addition of valsartan to standard HFrEF therapy (including ACEIs but not beta blockers) did not improve survival but reduced the incidence of the composite endpoint of morbidity and mortality, largely through decreased HF hospitalizations.</i> |

| | |
|---|--|
| CHARM (2004) | <p>4576 patients with CHF NYHA class II-IV with LVEF of $\leq 40\%$ were randomized to candesartan or placebo in 2 complementary parallel trials (CHARM-Alternative, for patients who cannot tolerate ACE inhibitors, and CHARM-Added, for patients who were receiving ACE inhibitors).</p> <p>Candesartan significantly reduces all-cause mortality, cv death, and HF hospitalizations when added to standard therapies including ACEIs, β-blockers, and an aldosterone antagonist.</p> |
| Post-MI heart failure: | |
| ARBs are second line to ACE-I (i.e. ACE-I-intolerant patients); valsartan may be considered for patients with post-MI heart failure | |
| VALIANT (2003) | <p>In patients ≥ 60 years with congestive HF with NYHA class II-IV, losartan was not associated with improved survival compared to captopril in elderly HF patients, but was significantly better tolerated.</p> |
| CV risk reduction: | |
| ARBs are second line to ACE-I (i.e. ACE-I-intolerant patients); telmisartan may be considered in all patients with symptomatic or asymptomatic CVD. | |
| ONTARGET (2008) | <p>Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.</p> |
| Hypertension: | |
| ARBs are second line to ACE-I (i.e. ACE-I-intolerant patients) for non-black patients aged <55 years. | |
| LIFE (2002) | <p>In participants aged 55-80 years with essential hypertension (BP 160-200/95-115 mmHg) and LVH ascertained by ECG, losartan seems to confer benefits beyond reduction in blood pressure.</p> |
| VALUE (2003) | <p>13,449 patients ≥ 50 years old with hypertension were either randomized to amlodipine- or to valsartan-based antihypertensive therapy. HCTZ and other medications were added as needed to achieve a target of $<$</p> |

| | |
|--|---|
| | <i>140/90mmHg. Patients were followed for 30 months. BP control was achieved in both groups, but BP was slightly lower in the amlodipine-based group.</i> |
|--|---|

Adverse effects:

- *Symptomatic hypotension*: rare but may occur, particularly if there is intravascular volume depletion. Avoid excessive diuretic doses.
- *Angioedema*: has been reported rarely with ARBs. Particular caution should be taken when initiating an ARB in a patient with a history of angioedema of any cause.

Contraindications:

- Hypersensitivity to ARBs
- Pregnancy and Breast-feeding

Cautions:

- Bilateral renal artery stenosis
- Aortic or mitral valve stenosis
- Hypertrophic cardiomyopathy
- Prior angioedema of any cause
- Hypotension (systolic blood pressure <90 mmHg)
- Patients on high-dose diuretics (i.e. furosemide >80 mg daily)
- Moderate to severe renal impairment (i.e. creatinine >150 µmol/L or eGFR <60 mL/min/1.73 m²).

Monitoring:

- Check BP and U&Es within two weeks of initiation or change of dose, then annually
- If serum creatinine increases by more than 20% (or eGFR falls by more than 15%) after initiation, stop ARB.

- ARB dose should only be increased if:
 - Systolic blood pressure >90 mmHg
 - Serum creatinine increases by less than 20% (or eGFR falls by less than 15%) on each dose titration
 - Potassium is <5.5 mmol/L.
- Hyperkalaemia: reduce dose if $K^+ > 5.5$ mmol/L; withdraw ARB if $K^+ > 6$ mmol/L.

Drug interactions:

- *Ciclosporin*: increases risk of hyperkalaemia
- *Lithium*: increases lithium levels.

Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

Sacubitril/valsartan

Mechanism of action:

Combination is an angiotensin receptor-neprilysin inhibitor (ARNI):

- **Sacubitril:** is neprilysin inhibitor, so inhibiting the degradation of natriuretic peptides (NPs), bradykinin. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP:
 - Enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling.
 - Inhibiting renin and aldosterone secretion.
 - decreased plasma MR-proANP and NT-proBNP.
- **Valsartan:** is Angiotensin II receptor type I inhibitor; decreases blood pressure and blocks vasoconstrictor and aldosterone-secreting effects of angiotensin II (reduces sodium and water retention and myocardial hypertrophy).

N.B: Previous attempts to treat heart failure with a neprilysin inhibitor alone were unsuccessful, possibly because the inhibition of angiotensin II breakdown antagonises the beneficial effects on NP. Combining a neprilysin inhibitor with an ACE inhibitor increased the risk of angioedema from dual inhibition of the breakdown of bradykinin. The combination of sacubitril with an angiotensin II receptor antagonist was therefore a logical next step, as only one of the enzymes responsible for breakdown of bradykinin is inhibited. The addition of sacubitril to valsartan produces greater vasodilation and natriuresis.

Indications & clinical evidence:

Table 36-34: Clinical trials of Sacubitril/valsartan:

| Trial (date) | Summary |
|--|---------|
| Heart failure with reduced ejection fraction: | |

| | |
|---|---|
| Indicated to reduce risk of cardiovascular death and hospitalization in chronic heart failure; benefits are most clearly evident in patients with HFrEF. | |
| PARADIGM-HF (2014) | <i>In patients with class II-IV heart failure and an EF \leq 40%, ARNI reduces CV mortality, all-cause mortality and HF hospitalizations when compared to enalapril.</i> |
| PARADISE-MI (2021) | <i>In patients with AMI, sacubitril/valsartan did not reduce the primary endpoint (CV death and HF hospitalization), compared with ramipril.</i> |
| EVALUATE-HF (2019) | <i>In patients with heart failure and LVEF \leq 40%, sacubitril-valsartan did not significantly reduce central aortic stiffness when compared with enalapril.</i> |
| LIFE (2021) | <i>In patients with advanced heart failure, the combination sacubitril/valsartan did not reduce NT-proBNP or clinical outcomes among patients with advanced HFrEF and comorbidities.</i> |
| Heart Failure with preserved Ejection Fraction: | |
| Sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with HFpEF. | |
| PARAGON-HF (2019) | <i>In patients with NYHA class II-IV heart failure, LVEF \geq 45%, elevated level of natriuretic peptides, and structural heart disease, sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes.</i> |
| PARAMOUNT (2012) | <i>In patients with NYHA class II-III heart failure, LVEF \geq 45%, and NT-proBNP $>$ 400 pg/mL, sacubitril–valsartan reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated.</i> |

Adverse effects:

- Hypotension (18%): Sacubitril/valsartan lowers blood pressure and may cause symptomatic hypotension; especially in patients who are volume-depleted or salt-depleted, or those taking diuretics.

- Hyperkalemia (12%): ARNI is associated with less renal dysfunction and hyperkalemia than ACEI.
- Cough (9%).
- Dizziness (6%).
- Falls (1.9%).
- Angioedema, all patients (0.5%); in black patients (2.4%).

Contraindications:

- Hypersensitivity to any component.
- Pregnancy: Discontinue as soon as possible when pregnancy is detected. Drug affects renin-angiotensin system, causing oligohydramnios, which may result in fetal injury or death.
- History of angioedema related to previous ACE inhibitor or ARB therapy. Coadministration of neprilysin inhibitors (eg, sacubitril) with ACE inhibitors may increase angioedema risk; do not administer ACE inhibitors within 36 hr of switching to or from sacubitril/valsartan.
- Concomitant use with aliskiren in patients with diabetes.
- eGFR < 30 mL/min/1.73 m².

Cautions:

- To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan.
- A prior history of angioedema with ACE-I contraindicates the use of sacubitril/valsartan, but a prior history of cough is not a contraindication.
- An increase in K⁺ up to ≤ 5.5 mmol/L is acceptable. If K⁺ rises to > 5.5 mmol/L, the ARNI should be stopped and specialist advice sought.
- There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition.

- Of note, neprilysin inhibitor is the only HF therapy that increases BNP, a consequence of its direct effect. This affects the diagnostic value of BNP, at least during therapy initiation, but BNP remains useful for monitoring in respect to the new baseline. Conversely, NT-pro- BNP is not directly affected.

Drug interactions:

- *Dual blockade of the renin-angiotensin-aldosterone system:*
 - Coadministration with an ACE inhibitor is contraindicated because of the increased risk of angioedema.
 - Avoid use with an ARB, because drug contains the angiotensin II receptor blocker valsartan.
 - Concomitant use with aliskiren is contraindicated in patients with diabetes.
- *Potassium-sparing diuretics:* Concomitant use of potassium-sparing diuretics (eg, spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.
- *NSAIDs* including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors):
 - In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with sacubitril/valsartan may result in worsening of renal function, including possible acute renal failure.
 - Effects are usually reversible; monitor renal function periodically.
- *Lithium:*
 - Increases in serum lithium concentrations and lithium toxicity have been reported during coadministration of lithium with angiotensin II receptor antagonists; monitor serum lithium levels.
 - Monitor renal function and potassium levels in susceptible patients (eg, diabetes, hypoaldosteronism, high-potassium diet, renal artery stenosis); dosage reduction or interruption may be required.

Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors

In 1996, investigators at Kyoto University and Tanuba Seiygyu Co. in Japan developed phlorizin analogs, the first chemically engineered sodium glucose co-transporter inhibitors (SGLT2is). In 2008, the FDA expressed concern about increased cardiovascular risk of new antidiabetic agents and shortly thereafter the EMA followed suit. The regulators required the sponsors of new anti-diabetic agents to demonstrate cardiovascular safety to gain approval. In 2015, the results of the first large placebo-controlled SGLT2i clinical outcome trial, EMPA-REG OUTCOME, in patients with T2DM and cardiovascular disease and reduced ejection fraction was reported. Quite unexpectedly, it showed that empagliflozin resulted in a significant 14% *reduction* of the primary endpoint (cardiovascular death, non-fatal myocardial infarction or stroke). Even more exciting were the 32% reduction in death from any cause, and the 35% reduction in hospitalization for heart failure.

Mechanism of action:

SGLT-2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen; SGLT2 inhibitors will reduce glucose reabsorption and lower the renal threshold for glucose, thereby increasing urinary glucose excretion.

Biological mechanisms and effects of SGLT-2 inhibitors in heart failure:

At present, the mechanisms underlying protective cardiovascular and renal effects of SGLT2 inhibitors in patients with/without T2DM are not completely understood, but several mechanisms have been proposed:

- **Metabolic and reno protective effects:**

- SGLT-2 inhibitors lower the threshold for glycosuria (60–90 g/day) by lowering the maximum renal transport capacity for glucose reabsorption ⁽¹⁾.
- SGLT2 inhibitors promote natriuresis and uricosuria.
- SGLT2 inhibitors increased insulin sensitivity and glucose uptake in the muscle cells, decreased gluconeogenesis and increased ketogenesis.
- SGLT2 inhibitors stimulate weight loss due to the renal caloric loss in glycosuria, and have a favourable impact on body fat distribution.
- SGLT2 inhibitors reduced liver steatosis and the accompanying hepatocellular injury.
- SGLT2 inhibitors provide nephron protection, most likely through a tubulo-glomerular feedback-mediated vasoconstriction of the afferent arteriole and the reduction in intra-glomerular pressure. This effect is important to reduce glomerular hyperfiltration in T2DM, which may decrease the risk of subsequent nephropathy.
- **Hemodynamic effects:** The favourable hemodynamic effects are mediated by a number of mechanisms including osmotic diuresis, natriuresis and plasma and interstitial fluid volume reduction, leading to a reduction in ventricular preload and afterload.

An increasing body of evidence suggests that SGLT2 inhibitors may less likely induce electrolyte disturbances, neurohormonal activation and a decline in renal function that can occur with diuretics.

In addition to hemodynamic effects, other mechanisms may be involved in the increase in hematocrit. Given that an increase in hematocrit lasts longer compared with the increase in urine output after an SGLT2 inhibitor initiation, it has been suggested that an increase in renal erythropoietin production could be a potential mechanism for the change in hemoglobin and hematocrit levels.

- **Cardiac effects:**

- SGLT2 inhibitors inhibit the sodium-hydrogen exchanger (NHE1) activity, which is up-regulated both in T2DM and HF. By inhibiting the NHE1 receptors, SGLT2 inhibitors may protect the heart from toxic intracellular Ca²⁺ overload.

(1) This effect attenuates at low glucose levels, explaining the low risk of hypoglycaemia with SGLT2 inhibitors.

- SGLT2 inhibitors exert direct effects on myocardial metabolism and decrease myocardial oxidative stress.
- Similar to T2DM, HF is characterized by a state of insulin resistance. In the insulin-resistant heart, free fatty acids are favoured as an energy source over glucose. This metabolic shift results in decreased cardiac metabolic efficiency (i.e. insufficient ATP production). Empagliflozin increased cardiac ATP production without changing overall metabolic efficiency.
- A benefit on ventricular remodelling was demonstrated in patients with T2DM and CAD in the EMPA-HEART CardioLink-6 study, which showed a reduction in LV mass index (as measured by CMR) and an improvement in diastolic function without changes in LV systolic function after 6 months of empagliflozin.
- Another unproven hypothesis includes possible cardiac anti-fibrotic effects.

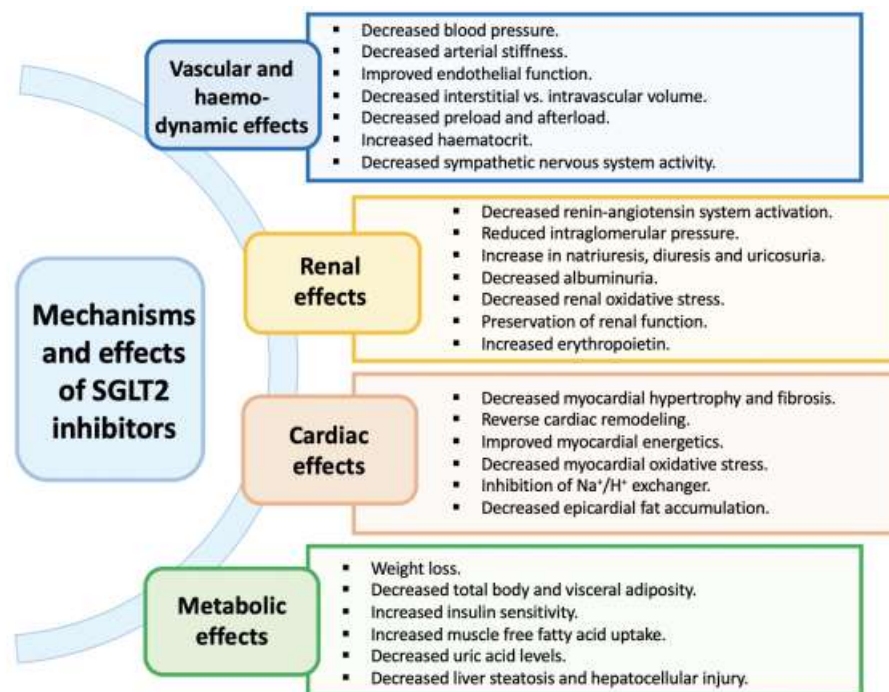


Figure 36-8: Biological mechanisms and effects of SGLT2 inhibitors. Source: Seferović PM, Fragasso G, Petrie M, et al. Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2020 Sep;22(9):1495-503.

Indications & clinical evidence:

Table 36-35: Clinical trials of SGLT2 inhibitors:

| Trial (date) | Summary |
|--|---------|
| Heart Failure with reduced ejection fraction: | |

| | |
|---|---|
| Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in adults with HF (NYHA class II-IV) with reduced ejection fraction | |
| DAPA-HF (2019) | <i>Among individuals with HFrEF (NYHA II-IV, LVEF $\leq 40\%$) with or without T2DM, the addition of dapagliflozin decreased rates of CV mortality or worsening HF, as well as all-cause mortality.</i> |
| EMPEROR-Reduced (2020) | <i>In patients with class II-IV heart failure and EF $\leq 40\%$, empagliflozin had a lower risk of CV mortality or HF hospitalization than those in the placebo group, regardless of the presence or absence of diabetes.</i> |
| SCORED (2021) | <i>In patients with type 2 DM (HbA1c $\geq 7\%$), CKD (eGFR = 25-60 ml/min/1.73 m²), and risks for CV disease, sotagliflozin resulted in a lower risk of the composite of CV mortality, HF hospitalizations, and urgent visits for HF but was associated with adverse events.</i> |
| Heart Failure with preserved ejection fraction: | |
| EMPEROR-Preserved (2021) | <i>In patients with class II-IV heart failure and LVEF $> 40\%$, empagliflozin reduced the combined risk of CV mortality or HF hospitalization, regardless of the presence of DM.</i> |
| DELIVER (2022) | <i>Dapagliflozin reduced the combined risk of worsening HF or CV mortality among patients with heart failure and a mildly reduced or preserved ejection fraction.</i> |
| Acute Decompensated Heart Failure: | |
| SOLOIST-WHF (2021) | <i>In patients with type 2 DM recently hospitalized for worsening HF, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of CV mortality and hospitalizations and urgent visits for heart failure than placebo.</i> |
| EMPULSE (2022) | <i>Among patients with acute decompensated heart failure, empagliflozin versus placebo was associated with significant clinical benefit at 90 days regardless of LVEF or diabetes status.</i> |
| Chronic Kidney Disease (CKD): | |

| | |
|--|--|
| Indicated to reduce risk of sustained eGFR decline, end-stage kidney disease (ESKD), cardiovascular death, and hospitalization for HF in adults with CKD who are at risk of progression. | |
| DAPA-CKD (2020) | <i>Among patients with CKD (eGFR 25-75 ml/min/1.73 m²) and a urinary albumin-to-creatinine ratio 200-5000), regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes was significantly lower with dapagliflozin than with placebo.</i> |
| EMPA-KIDNEY (2023) | <i>Among a wide range of patients with CKD (eGFR 20-45 ml/min/1.73 m², or who had an eGFR 45-90 ml/min/1.73 m² with a urinary albumin-to-creatinine ratio ≥ 200), empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.</i> |

Adverse effects:

- Urinary tract infection.
- Glycosuria (as the consequence of dapagliflozin action) may predispose to Genital mycotic infections.
- Increase risk of ketoacidosis in patients with type 1 and type 2 diabetes mellitus ⁽¹⁾.
- Nasopharyngitis.
- SGLT2i have a relatively weak effect on blood pressure. Symptomatic hypotension may occur after initiating, particularly in patients with renal impairment (eGFR < 60 mL/min/1.73 m²), with low systolic blood pressure, taking loop diuretics, or who are elderly.
- Back pain.
- Increased urination.

(1) Rather than contraindicating patients at risk of ketoacidosis, the Canadian Diabetes Association Clinical Practice recommended that insulin should be stabilized in patients with insulin deficiency before starting an SGLT2i, and SGLT2i should be withheld only when a precipitating factor of ketoacidosis occurs (acute illness, surgery, dehydration or excessive alcohol intake).

- Necrotizing fasciitis of the perineum (Fournier gangrene) reported with SGLT2 inhibitors; signs and symptoms include tenderness, redness or swelling of the genitals, or area from the genitals to the rectum.

Contraindications:

- Serious hypersensitivity to dapagliflozin (e.g, anaphylaxis, angioedema)
- End-stage renal disease and/or on haemodialysis: Sotagliflozin and dapagliflozin can be initiated only in patients with eGFR of >25 mL/min/ 1.73 m², whereas empagliflozin can be initiated to 20 mL/min/ 1.73 m². However, there are no data on the use of SGLT2is in patients with end-stage renal disease and/or on haemodialysis.

Cautions:

- The FDA recommends stopping canagliflozin, dapagliflozin, and empagliflozin 3 days and ertugliflozin at least 4 days before scheduled surgery (due to elevated risk of euglycemic DKA).
- Hypoglycemia risk increased with insulin and insulin secretagogues (e.g, sulfonylureas); a lower dose of insulin or insulin secretagogue may be required.
- Type 1 diabetes mellitus is not an absolute contraindication. Although reassuring results have been reported from the SGLT2i experience in patients with type 1 diabetes, the available level of evidence is insufficient to permit the use of SGLT2i in this population.
- Urine glucose tests is not recommended in patients taking SGLT2 inhibitors, as SGLT2 inhibitors, increase urinary glucose excretion and lead to positive urine glucose tests; use alternative methods to monitor glycemic control.
- 1,5-AG assay is not recommended, as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors; use alternative methods to monitor glycemic control.
- Increase in LDL-cholesterol compared with placebo.

Guanylate cyclase Stimulator

Vericiguat

Mechanism of action:

In HF, there is a change in nitric oxide synthesis as well as a decrease in the activity of its receptor, soluble guanylate cyclase (GC), which in turn causes a cyclic guanosine monophosphate (cGMP) deficiency. The cGMP deficiency causes deterioration in myocardial, vascular, and renal function.

Vericiguat is an oral drug that directly stimulates GC, which increases the availability of intracellular cGMP and thus produces beneficial effects, including a reduction in LV remodeling, an improvement in myocardial and vascular function, and a decrease in fibrosis and inflammation.

Indications & clinical evidence:

Table 36-36: Clinical trials of Vericiguat:

| Trial (date) | Summary |
|--|--|
| Vericiguat should be considered in symptomatic patients who present with worsening of HF despite first-line treatment to reduce the risk of cardiovascular death or hospitalization due to HF. | |
| VICTORIA (2020) | <i>In patients with chronic heart failure NYHA II-IV and EF ≤ 45% with recent hospitalization and eGFR ≥ 15 mL/min/1.73 m², vericiguat reduced CV mortality or HF hospitalization by 10%.</i> |
| VITALITY (2020) | <i>In patients with HFpEF after recent decompensation, vericiguat did not improve the physical limitation score (PLS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 24 weeks.</i> |

Adverse effects:

Hypotension

Contraindications:

- Pregnancy (may cause fetal harm).
- Concomitant use of vericiguat and phosphodiesterase 5 inhibitors or other GC stimulators (such as riociguat) is contraindicated.
- Starting vericiguat is not recommended in patients with systolic BP < 100 mmHg. For symptomatic hypotension, reducing/suspending the dose of vericiguat is recommended, according to the case.

Cautions:

- Before beginning treatment with vericiguat after an episode of HF decompensation, it is recommended to optimize the volemic/diuretic status, in particular in patients with very high NT-proBNP levels.
- Absolute bioavailability is high when taken with food (93%), so taking with food is recommended.
- The use of vericiguat in subjects with more advanced kidney disease or severe liver failure has not been studied (It is also not necessary to adjust the dose in subjects with a GFR ≥ 15 mL/min/1.73 m² or with mild or moderate liver failure).
- Exclude pregnancy before initiating it.

Drug interactions:

- With respect to metabolism, glucuronidation through UGT1A9 and UGT1A1 is the main pathway of biotransformation, whereas the metabolism mediated by the cytochrome P450 is small (<5%). Therefore, the risk of pharmacokinetic interactions with other drugs is low.
- Concomitant use of vericiguat and other GC stimulators such as riociguat is contraindicated.
- Concomitant use of vericiguat and phosphodiesterase 5 inhibitors is contraindicated.

Riociguat

Will be discussed later in Pulmonary arterial hypertension specific therapy.

Diuretics

Classification of diuretics:

- **Carbonic Anhydrase Inhibitors:** Acetazolamide (used in glaucoma, acute mountain sickness and metabolic alkalosis) ⁽¹⁾.
- **Osmotic Diuretics:** Mannitol.
- **Loop diuretics:** Furosemide, Torsemide, Bumetanide.
- **Thiazide and Thiazide-Like diuretics:** Hydrochlorothiazide, Chlorthalidone, Metolazone, Indapamide.
- **Potassium sparing diuretics:** Amiloride, Triamterene, Spironolactone, Eplerenone.

(1) *Due to haemodynamic alterations in heart failure with a reduction in renal blood flow with a correspondingly increased filtration fraction, important increases in proximal nephron sodium avidity occur. From a pathophysiological point of view, targeting sodium reabsorption in the proximal tubules has several potential benefits in heart failure. The carbonic anhydrase inhibitor acetazolamide inhibits sodium reabsorption in the proximal tubules. A multicentre, randomized, double-blind, (ADVOR) trial will investigate if combination therapy with acetazolamide improves loop diuretic response to increase diuresis in decompensated heart failure patients.*

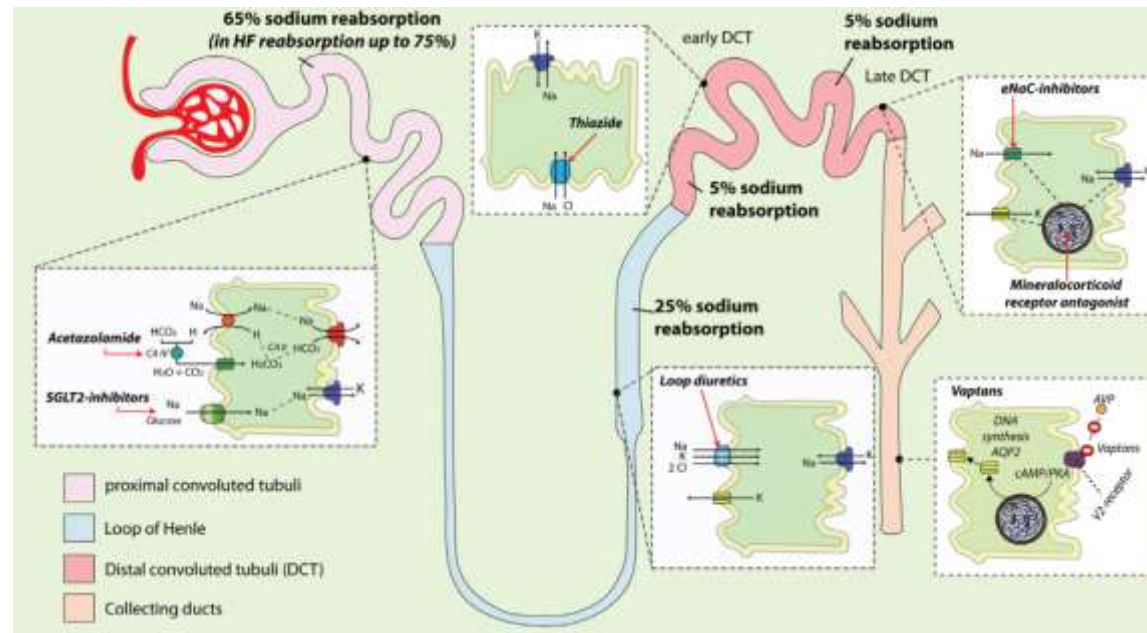


Figure 36-9: Sites and mode of action and effects on sodium reabsorption in the nephron of different diuretics. AQP2, aquaporin-2; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; eNaC, epithelial sodium channel; PKA, protein kinase A; SGLT2, sodium–glucose linked transporter-2. **Source:** Mullens W., Damman K., Harjola V., et al. The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure* (2019) 21, 137–155. doi:10.1002/ejhf.1369

| Table 36-37: Pharmacology of diuretics: | | | | | |
|---|---|--|---|---|---|
| | Acetazolamide | Loop diuretics | Thiazide-like diuretics | MRA ⁽¹⁾ | Amiloride |
| Site of action | Proximal nephron | Ascending loop of Henle | Early distal convoluted tubule | Late distal tubule | Late distal tubule |
| Starting/usual dose | Oral: 250–375 mg Intravenous: 500 mg | Furosemide: 20–40/40–240 mg ⁽²⁾ Bumetanide: 0.5–1.0/1–5 mg Torsemide: 5–10/10–20 mg | HCTZ: 25/12.5–100 mg ⁽³⁾ Metolazone: 2.5/2.5–10 mg Chlorthalidone: 25/25–200 mg Chlorothiazide: 500–1000 mg | Spironolactone: 25/25–50 mg Eplerenone: 25/25–50 mg Potassium canrenoate: 25–200mg. not for chronic use | 5/10 mg |
| Max. total daily dose | Oral: 500 mg 3x/day Intravenous: 500 mg 3x/day | Furosemide: 400–600 mg Bumetanide: 10–15 mg Torsemide: 200–300 mg | HCTZ: 200 mg Metolazone: 20 mg Chlorthalidone: 100 mg Chlorothiazide: 1000 mg | 50–100 mg (doses up to 400 mg are used in hepatology) | 20 mg |
| Half-life | 2.4–5.4 h | Furosemide: 1.5–3.0 h Bumetanide: 1–1.5 h Torsemide: 3–6 h | HCTZ: 6–15 h Metolazone: 6–20 h Chlorthalidone: 45–60 h | Canrenone: 16.5 h ⁽⁴⁾ Eplerenone: 3–6 h | Normal GFR: 6–9 h GFR < 50: 21–144 h |

(1) Minimal diuretic effect.

(2) Dose of intravenous and oral loop diuretics are similar.

(3) Only PO use in acute HF, thiazides are not recommended for daily ambulatory use in chronic stable HF.

(4) Canrenone is the active metabolite of spironolactone. IV potassium canrenoate is the IV formulation and is metabolized to canrenone resulting in significant plasma levels after 2.5 h.

| | | | | | |
|--|--|---|--|--|------------------------------|
| Onset | PO: 1 h IV: 15–60 min | PO: 0.5–1 h IV: 5–10 min SC: 0.5 h | PO: 1–2.5 h IV: Chlorothiazide is IV available, onset action: 30 min | PO: 48–72 hd IV: potassium canrenoate; 2.5h | PO: 2 h IV: not available |
| Oral bioavailability | Absorption is dose-dependent, dose >10 mg/kg exhibit variable uptake | Furosemide: 10–100% Bumetanide: 80–100% Torsemide: 80–100% | HCTZ: 65–75% Metolazone: 60–65% ⁽¹⁾ Chlorothiazide: 9–56% | Spironolactone: ~90% Eplerenone: 69% | 30–90% |
| Enteral absorption affected by Food | May be taken with food. Food decreases symptoms of GI upset. | Furosemide: yes (slowed) Bumetanide: yes (slowed) Torsemide: no | HCTZ: unknown Metolazone: unknown Chlorthalidone: unknown | Spironolactone: bioavailability increase with high fat food Eplerenone: unknown | Unknown |
| Potency (FENa%)⁽²⁾ | 4% | 20-25% | 5-8% | 2% | 2% |

(1) Variations between pharmaceutical brands of metolazone exist.

(2) Tested in non-HF patients. FENa is the percentage of the sodium filtered by the kidney, which is ultimately excreted in the urine. It is measured based on plasma and urinary sodium. In clinical use, FENa can be calculated as part of the evaluation of diuretic effectiveness. The normal value depends primarily on the GFR of the patient but is commonly < 2% in patients with relatively intact renal function. Diuretic agents increase FeNa with loop diuretic agents to be the most potent ones. $FENa = 100 \times (Na \text{ urine} \times creatinine \text{ plasma}) / (Na \text{ plasma} \times creatinine \text{ urine})$.

Loop diuretics

(Furosemide, Torsemide, Bumetanide)

Mechanism of action:

Inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter associated with the transport of chloride across the lining cells of the ascending limb of the loop of Henle. This site of action is reached intraluminally, after the drug has been excreted by the proximal tubule. The effect of the cotransport inhibition is that chloride, sodium, potassium, and hydrogen ions all remain intraluminally and are lost in the urine. In comparison with thiazide-type diuretics, there is a relatively greater urine volume and relatively less loss of sodium. The consistency of torsemide's absorption (80-100%) and its longer duration of action are distinguishing features among loop diuretics.

Adverse effects:

- Hyperuricemia (40%).
 - Consider allopurinol prophylaxis (not initiated during acute exacerbation).
 - For symptomatic gout use colchicine for pain relief. Avoid NSAIDs.
- Hypokalemia (14-60%).
- Glucose intolerance.
- Hearing impairment and tinnitus: Inhibition of an isoform of the $\text{Na}/\text{K}/\text{2Cl}$ transporter expressed by hair cells of the inner ear is believed to be responsible for the rare incidence of ototoxicity.

Cautions:

- Use caution in systemic lupus erythematosus (May exacerbate lupus), liver disease, renal impairment.
- IV route twice as potent as PO.
- Food delays absorption but not diuretic response.
- Possibility of skin sensitivity to sunlight.

- Risk of ototoxicity is increased with hypoproteinemia; it is associated with rapid injection, severe renal impairment, use of high doses, concomitant use of aminoglycosides, or other ototoxic drugs.
- High doses (> 80 mg) of furosemide may inhibit binding of thyroid hormones to carrier proteins and result in transient increase in free thyroid hormones, followed by decrease in total thyroid hormone.

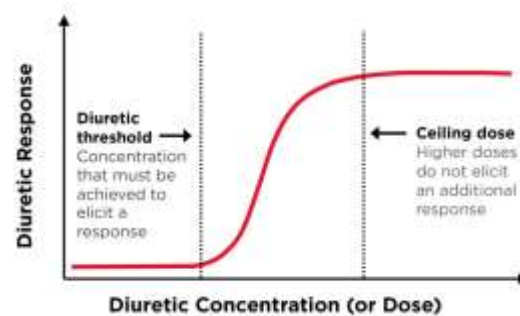


Figure 36-10: Sigmoid dose-response curve for loop diuretic therapy with a threshold dose and ceiling dose. Doses smaller than the threshold dose produce little or no diuretic effect. Loop diuretics also have a ceiling dose. This is the dose that shows the maximum fractional sodium excretion. Doses higher than the ceiling dose start to yield diminishing returns and are only slightly more effective. Increasing the frequency of dosing with the ceiling dose is more effective than increasing the dose. Both the threshold and ceiling dose varies depending on the patient characteristics.

Thiazide and thiazide-like diuretics

(Hydrochlorothiazide, Chlorthalidone, Metolazone, Indapamide)

Mechanism of action:

Thiazides are sulfonamide related organic acids that are secreted into the proximal tubule by an organic secretory mechanism, then inhibits sodium reabsorption at the beginning of the *distal convoluted tubule* by blocking the $\text{Na}^+\text{-Cl}^-$ symporter. Increased sodium reaches the distal tubules to stimulate exchange with potassium, particularly in the presence of an activated renin-angiotensin-aldosterone system. Thiazides may also increase the active excretion of potassium in the distal renal tubule.

Thiazide-type diuretics as a class differ from the loop diuretics in that they have a longer duration and site of action. Additionally, thiazides are so-called low-ceiling diuretics, because the maximal response is reached at a relatively low dose and they demonstrate a decreased capacity to exert a predictable in the presence of renal failure. The fact that thiazides and loop diuretics act at different tubular sites explains their additive effects, termed *sequential nephron block*.

Indications:

- **Hypertension:** Thiazide diuretics remain among the medication classes recommended for first-line therapy for hypertension. Lower doses (25-50 mg) exert as much antihypertensive effect as larger doses (although thiazides are more natriuretic at higher doses).
- **Heart Failure:** Thiazides have been found to be the best drugs for prevention of heart failure in patients with hypertension (superior to ACE-I, alpha blockers & CCBs). (SHEP & ALLHAT clinical trials).
- **Kidney Stones (Calcium subtype):** roughly 2/3 of kidney stones are rich in calcium phosphate or calcium oxalate, and a high percentage of such patients have a defect in proximal calcium reabsorption. Thiazide diuretics increase calcium reabsorption in the distal convoluted tubule, and can lower urinary calcium excretion by as much as 50%, resulting in up to a 90% reduction in the incidence of new stones.

- **Nephrogenic Diabetes Insipidus:** Nephrogenic DI results from renal insensitivity to the effects of ADH, resulting in polyuria. It can be either congenital (due to inherited genetic defects), or acquired (most commonly caused by hypercalcemia, or chronic therapy with lithium). Urine output in such patients can be reduced with a low sodium diet, NSAIDs and thiazide diuretics.

Adverse effects:

- Postural hypotension
- Hyponatraemia
- Hypokalaemia: Thiazides can induce significant kaliuresis, as per sodium ion lost 2–3 ions of potassium are excreted. This potassium losing effect is especially pronounced in high aldosterone states, such as heart failure. The incidence of hypokalemia is dose-dependent, and is < 25% in patients on standard low-dose therapy with thiazides.
- Hypercalcaemia
- Gout
- Impaired glucose tolerance: There is evidence that the hyperglycemia may be related to loss of body potassium, which may affect the ability of pancreatic beta cells to regulate the release of insulin via ATP sensitive K channels. Correction of hypokalemia can reverse thiazide-induced hyperglycemia.
- Hyperlipidemia Dyslipidemia can be produced by high doses of thiazides (not typically used). The mechanism by which thiazides and some beta blockers affect lipid levels is still poorly understood.
- Impotence

Cautions:

- Use with caution in diabetes mellitus, hypercholesterolemia, hyperuricemia or gout, hypotension, systemic lupus erythematosus (can cause exacerbation or activation), previous sympathectomy, liver disease.
- Patients allergic to sulfa may show cross-sensitivity.
- In primary adrenal insufficiency, avoid use of diuretics to treat hypertension.

- Therapy with metolazone may render the patients volume depleted if given in the morning of surgery.

Drug interactions:

- Avoid concurrent use with lithium (reduction of lithium dosage by 50% may be necessary).
- May aggravate digitalis toxicity.

Potassium Sparing diuretics

(Amiloride, Triamterene, Spironolactone, Eplerenone)

Potassium Sparing diuretics are two types:

- **Aldosterone Receptor Antagonists:**
 - **Steroidal MRA:** Spironolactone, Eplerenone.
 - **Non-steroidal MRA:** Finerenone.
- **Epithelial Na channels (ENaC) Blockers:** Amiloride, Triamterene.

Mechanism of action:

- **Aldosterone antagonists** are structurally similar to aldosterone, act as competitive binding of receptors at aldosterone-dependent Na-K exchange site in distal tubules results in increased excretion of Na⁺, Cl⁻, and water and retention of K⁺ and H⁺. Spironolactone increases testosterone clearance and estradiol production; blocks conversion of potent androgens to weaker ones in peripheral tissues. Spironolactone is a pro-drug with onset of action only 48-72 h after oral intake.
- **ENaC Blockers:** Direct effect on renal distal tubule to inhibit Na⁺ reabsorption. Inhibits Na/K-ATPase, decreases Ca⁺⁺, Mg⁺⁺ and hydrogen excretion.

Indications and Clinical evidence:

Table 36-38: Clinical trials of Mineralocorticoid Receptor Antagonists:

| Trial (date) | Summary |
|---|---------|
| Heart Failure: | |
| Spironolactone is indicated as an adjunct to standard therapy (ACE-I, B-blocker plus diuretic) at low doses in patients with moderate to severe heart failure. Eplerenone may be considered as an alternative in patients unable to tolerate spironolactone first line usually due to the development of gynaecomastia. | |

| | |
|--|--|
| RALES (1999) | <i>In patients who had severe heart failure and LVEF < 35%, spironolactone led to a 30% reduction in all-cause mortality.</i> |
| EPHESUS (2003) | <i>In patients with acute MI complicated by LV dysfunction and HF symptoms, eplerenone reduced the rate of mortality.</i> |
| EMPHASIS-HF (2011) | <i>In patients with NYHA class II heart failure and EF < 35%, eplerenone reduces the risk of death and hospitalization.</i> |
| Post-MI heart failure: | |
| Eplerenone should be prescribed within 3–14 days of MI, preferably after initiation of ACE-I therapy, for patients with symptoms and/or signs of heart failure with an EF < 40%. | |
| EPHESUS (2003) | <i>In patients with acute MI complicated by LV dysfunction and heart failure, eplerenone, added to optimal medical therapy, reduces morbidity and mortality among patients.</i> |
| Finerenone in Kidney Disease and Type 2 Diabetes: | |
| FIDELIO-DKD (2020) | <i>In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.</i> |
| FIGARO-DKD (2021) | <i>Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo.</i> |

Adverse effects:

- *Hyperkalaemia*: this is common. Patients should be advised to avoid foods that are high in potassium bananas, tomatoes, citrus fruit, Lo-Salt. Dose reduction, or even drug withdrawal, may be necessary.

- *Renal dysfunction*: renal decline is common following initiation of spironolactone or eplerenone, particularly if already treated with ACE-I and diuretics. Careful control of fluid balance is essential. Dose reduction, and in some cases drug withdrawal, may be required.
- *Gynaecomastia*: Spironolactone can cause gynaecomastia (enlargement of glandular tissue in the male breast) due to effects on estrogen steroid receptors. Due to its greater selectivity for mineralocorticoid receptors, eplerenone has not been associated with this side effect.
- *Gastrointestinal*: diarrhea, constipation, nausea, vomiting, and abdominal discomfort.
- *Menstrual irregularities*.
- *Rashes*.

Contraindications:

- Hypersensitivity to spironolactone or eplerenone.
- Serum K^+ > 5.0 mmol/L at initiation.
- Moderate to severe renal insufficiency.
- Anuria.
- Severe hepatic insufficiency

Cautions:

- Hepatic impairment (monitor electrolytes closely).
- Significant renal dysfunction (creatinine > 2.5 mg/dL or eGFR < 30 mL/min/1.73 m²). If K^+ rises to > 6.0 mmol/L or creatinine to > 3.5 mg/dL or eGFR < 20 mL/min/1.73 m², stop MRA immediately and seek specialist advice.
- Pregnancy and lactation.
- Elderly.

Monitoring:

- Check baseline blood chemistry and blood pressure.
- Check blood chemistry within a week (e.g., serum creatinine, urea, potassium, sodium) of starting therapy or dose adjustment and again after a month of therapy or dose adjustment.
- Monitoring is recommended at least 3 monthly thereafter.

Drug interactions:

- *ACE-Is and ARBs*: increased risk of severe hyperkalemia with aldosterone antagonists.
- *Alpha-blockers*: enhanced hypotensive effect
- *Antiarrhythmic drugs*: plasma levels of eplerenone increased by amiodarone, so reduce eplerenone dose.
- *Antibacterial drugs*: plasma levels of eplerenone increased by clarithromycin, so avoid concurrent use.
- *Antidepressants*: plasma levels of eplerenone reduced by St Johns Wort, so avoid concurrent use.
- *Anti-epileptic drugs*: plasma levels of eplerenone reduced by carbamazepine and phenytoin, so avoid concurrent use.
- *Antifungal drugs*: plasma levels of eplerenone increased by itraconazole and ketoconazole.
- *Antiviral drugs*: plasma levels of eplerenone increased by nelfinavir and ritonavir—avoid concomitant use; also by saquinavir, so reduce eplerenone dose.
- *Cardiac glycosides*: spironolactone may increase plasma levels of digoxin.
- *Ciclosporin*: increased risk of hyperkalaemia
- *Lithium*: increased lithium levels with associated increased risk of toxicity
- *Potassium salts*: increased risk of hyperkalaemia
- *Tacrolimus*: increased risk of hyperkalaemia.

B blockers

Classification of b-blockers

- **β -Blockers can be classified according to selectivity into ⁽¹⁾:**
 - **Nonselective agents** (those producing a competitive blockade of both β_1 - and β_2 -adrenergic receptors): Propranolol, Sotalol (Antiarrhythmic β -blockers), Nadolol, Timolol
 - **β_1 -selectivity (Cardioselective agents):** Acebutolol, Atenolol, Bisoprolol, Metoprolol, Esmolol (Ultrashort-Acting IV β -Blockade)
 - **Vasodilating β -blockers:** mediated via:
 - α_1 -adrenoceptor blockade: Carvedilol, Labetalol.
 - β_2 -adrenergic receptor agonism: Celiprolol
 - via mechanisms independent of the adrenoceptor blockade: Bucindolol, Nebivolol.
- **β -Blockers can be classified into:**
 - **Lipophilic drugs:**

Lipophilic drugs (metoprolol, propranolol, timolol) are rapidly and completely absorbed from the GIT but are extensively metabolized in the gut wall and in the liver (first pass effect), so that their oral bioavailability is low (10-30%). These drugs may accumulate in patients with reduced hepatic blood flow (i.e., elderly, congestive heart failure, liver cirrhosis). Lipophilic drugs present short elimination half-lives (1-5 h) and they easily enter the CNS, which may account for a greater incidence of central side-effects.
 - **Hydrophilic drugs:**

Hydrophilic drugs (atenolol, esmolol) are absorbed incompletely from the gastrointestinal tract and are excreted unchanged or as active metabolites by the kidney. They have longer half-lives (6–24 h), and do not interact with other liver-metabolized

(1) Selectivity is dose dependent and decreases or disappears when larger doses are used.

drugs. They barely cross the blood–brain barrier. Elimination half-life is increased when glomerular filtration rate is reduced (i.e., elderly, renal insufficiency).

○ **Balanced clearance drugs:**

- Bisoprolol has a low first-pass metabolism, enters the CNS and is excreted in equal proportion by hepatic and renal routes.
- Carvedilol has a low oral bioavailability due to an extensive first pass effect. It binds to plasma proteins and is eliminated by hepatic metabolism.
- Esmolol is an ultra short-acting drug. It is administered i.v. (half-life 9 min).

| Table 36-39: Pharmacological classification of commonly used b-blockers: | | | | |
|--|---|------------------|-------------------------|----------------------------|
| β -blocker | Intrinsic Sympathomimetic Activity ⁽¹⁾ | Lipid solubility | Peripheral vasodilation | Average daily oral dose |
| Non-selective ($\beta_1 + \beta_2$) blockers: | | | | |
| <i>Carteolol</i> | + | Low | | 2.5–20 mg once/twice daily |
| <i>Nadolol</i> | 0 | Low | | 40–320 mg once daily |
| <i>Penbutolol</i> | + | Moderate | | 20–80 mg once/twice daily |
| <i>Pindolol</i> | ++ | High | | 10–40 mg twice daily |
| <i>Propranolol</i> | 0 | High | | 40–180 mg twice daily |
| <i>Sotalol</i> | 0 | Low | | |
| <i>Timolol</i> | 0 | High | | 5–40 mg twice daily |
| Selective β_1-blockers: | | | | |

(1) Intrinsic sympathomimetic activity: β -blockade mainly occurs during catecholamine surges; these agents do not decrease mortality and are preferably avoided.

| | | | | |
|--|---|----------|---|--------------------------------|
| <i>Acebutolol</i> | + | Moderate | | 200–800 mg once/twice daily |
| <i>Atenolol</i> | 0 | Low | | 25–100 mg once daily |
| <i>Betaxolol</i> | 0 | Moderate | | 5–20 mg once daily |
| <i>Bisoprolol</i> | 0 | Moderate | | 2.5–10 mg once daily |
| <i>Celiprolol</i> | + | Moderate | + | 200–600 mg once daily |
| <i>Esmolol</i> | 0 | Low | | Only i.v. |
| <i>Metoprolol</i> | 0 | High | | 50–100 mg once/twice daily |
| <i>Nevibolol</i> | 0 | | + | 2.5–5 mg once daily |
| α_1- and β-blockers: | | | | |
| <i>Bucindolol</i> | + | Moderate | + | 25–100 mg twice daily |
| <i>Carvedilol</i> | 0 | Moderate | + | 3.125–50 mg twice daily |
| <i>Labetalol</i> | + | Low | + | 200–800 mg twice daily |

Mechanism of action:

- Beta-blockers block the action of noradrenaline at B-adrenergic receptors, which are located in the myocardium, throughout the circulatory system and elsewhere. As a result, B-blockers inhibit sympathetic stimulation of heart rate and myocardial contractility and thus decreasing myocardial O₂ demands.

- Beta-blockers slow the firing of the pacemaker cells in the SA node and hence are negatively chronotropic, and also affect the conduction through the AV node. Thus, they also have anti-ischemic and anti-arrhythmic effects.
- Beta-blockers lower blood pressure, although the exact mechanism for this effect is unclear. It is postulated that reducing circulating renin levels or lowering sympathetic tone may be responsible.

Indications and Clinical evidence:

| Table 36-40: Clinical trials of β -Blockers: | |
|--|--|
| Trial (date) | Summary |
| Angina: | |
| β -blockers are highly effective to control exercise-induced angina, improve exercise capacity, and to reduce or suppress both symptomatic and asymptomatic ischaemic episodes. They may increase perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas. | |
| ASIST (1994) | <i>In patients with mild or no angina, abnormal exercise tests, and ischemia on ambulatory monitoring, atenolol treatment reduced daily life ischemia and was associated with reduced risk for adverse outcome compared with placebo.</i> |
| In Acute MI: | |
| Several large, long-term studies have demonstrated that the use of β -blockers in patients recovering from an AMI improves survival by 20-25% through a reduction of CV mortality, sudden cardiac death and reinfarction. | |
| ISIS-1 (1986) | <i>In patients after the onset of suspected AMI, early administration of beta blockade improves clinical outcome.</i> |
| MIAMI (1985) | <i>In patients with definite or suspected AMI, treatment with i.v metoprolol (15 mg) shortly after the patient's arrival in hospital within 24 h of the onset of symptoms, and then oral treatment (200 mg daily) was associated with less mortality rate than in placebo.</i> |
| Post-MI secondary prevention: | |

| | |
|---|--|
| β-blockers limit infarct size, reduce life-threatening arrhythmias, relieve pain and reduce mortality including sudden cardiac death. | |
| BHAT (1983) | <i>In patients after AMI, propranolol reduced mortality after mean follow-up of 2 years by 25%.</i> |
| Norwegian trial | <i>In patients after AMI, timolol reduced mortality from 9.8% to 7.2% over a follow-up of 25 months. Sudden cardiac death and reinfarction were also reduced. Interestingly, the beneficial influence of timolol on survival was sustained for at least 6 years.</i> |
| CAPRICORN (2001) | <i>In patients with a proven acute MI and a LVEF ≤ 40%, carvedilol reduced the frequency of all-cause and CV mortality, and recurrent, non-fatal MI.</i> |
| Heart failure: | |
| CIBIS-II (1999) | <i>In patients in NYHA class III or IV, with LVEF < 35% receiving standard therapy with diuretics and ACEI, bisoprolol 1.25 mg uptitrated to 10 mg reduced all-cause mortality, all-cause hospitalizations and sudden cardiac death.</i> |
| COPERNICUS (2002) | <i>In patients who had HF symptoms at rest or on minimal exertion, who were clinically euvolemic and who had an EF < 25%, carvedilol reduces risk of death or HF hospitalization by 31% compared to placebo in class III-IV HF with EF < 25%.</i> |
| CAPRICORN (2001) | <i>In patients with a proven AMI and LVEF ≤ 40%, carvedilol reduced the frequency of all-cause and CV mortality, and recurrent, non-fatal MI.</i> |
| MERIT-HF (1999) | <i>In patients with symptomatic HFrEF with EF ≤ 40%, long-acting metoprolol led to a 34% reduction in all-cause mortality.</i> |
| SENIORS (2005) | <i>In patients ≥ 70 years, with chronic heart failure (LVEF ≤ 35% within prior six months or hospital admission for chronic heart failure within prior year), nebivolol is an effective and well-tolerated treatment for heart failure in the elderly.</i> |

Adverse effects:

- *Bradycardia* (HR < 50 bpm): β -blockers reduce heart rate, decrease the firing rate of cardiac ectopic pacemakers and slow conduction and increase the refractory period of the AV node.
- *Symptomatic hypotension*: consider dose reduction, exclude heart block.
- *Bronchospasm*: review need for B-blocker and consider alternative drug class. If compelling indication, use a cardioselective B-blocker with extreme caution and under specialist supervision.
- *Central effects (fatigue, headache, sleep disturbances and depression)* are less common with hydrophilic drugs. In some patients the fatigue may be related to a decrease in blood flow to skeletal muscles; in other cases, it may be secondary to a central effect.
- *Cold extremities*: protect fingers and toes with gloves/socks in cold weather.
- *Sleep disturbances*: consider a water-soluble agent.
- *Erectile dysfunction*
- *Abrupt discontinuation of β -blockers after chronic treatment can lead to rebound symptoms (i.e., hypertension, arrhythmias, exacerbated angina). This increased risk is related with upregulation of β -adrenoceptors during chronic treatment.*

Contraindications:

- Asthma or history of bronchospasm
- PR interval > 0.24 s, any second- or third-degree AV block.
- Symptomatic hypotension
- Severe decompensated heart failure.
- Chronic obstructive lung disease without bronchospastic activity and peripheral vascular disease are not considered as absolute contraindications and high-risk patients may obtain a significant benefit from this therapy.
- Vasospastic angina
- Severe peripheral vascular disease: Severe PAD was considered a relative contraindication to non-selective β -blockers, because of an initial β_2 -blocker vasoconstrictive effect. However, this is no longer a contraindication to β -blockers, as they proved safe

in patients with PAD. Also, PAD patients often die of CAD, and thus, β -blockers are valuable in the PAD setting. However, individual responses may vary, and be aware of a potential worsening of severe rest symptoms.

Cautions:

- Chronic obstructive pulmonary disease (if evidence of a reversible component)
- Severe (NYHA class IV) HF.
- Current or recent (< 4 weeks) exacerbation of HF (e.g., hospital admission with worsening HF).
- If persisting signs of congestion, hypotension (SBP < 90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema—try to relieve congestion before starting a beta-blocker.
- Sick sinus syndrome
- Patients on diltiazem
- Bradycardia < 50 bpm: If < 50 b.p.m. and worsening symptoms, halve the dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary). Review the need for other heart rate-slowing drugs (e.g., digoxin, ivabradine, amiodarone, diltiazem, or verapamil).
- Peripheral vascular disease
- Pregnancy and breast feeding.

Monitoring:

- Obtain baseline BP and pulse before initiation and after dose changes.
- In the absence of side-effects review within 4 weeks and consider dose titration.
- Lethargy and/or impotence are not necessarily indications for drug withdrawal. Side-effects are frequently distressing but may wear off over time. Patient concerns should be addressed; however, they should be strongly encouraged to persevere with therapy in view of the cardiac benefits.
- If medication discontinuation proves necessary, withdraw B-blocker slowly to avoid reflex tachycardia.

Drug interactions:

- *Alpha-blockers*: enhanced hypotensive effect
- *Aluminium salts, cholestyramine, and colestipol* may decrease the absorption of *b*-blockers.
- *Alcohol, phenytoin, rifampicin, and phenobarbital, as well as smoking*, induce hepatic biotransformation enzymes and decrease plasma concentrations and elimination half-lives of lipophilic *b*-blockers.
- *Cimetidine and hydralazine* may increase the bioavailability of propranolol and metoprolol by reducing hepatic blood flow.
- *Anti-arrhythmics*:
 - Amiodarone—increased risk of myocardial depression, AV block and bradycardia
 - Flecainide—increased risk of myocardial depression and bradycardia
 - Lidocaine—increased risk of toxicity with propranolol
 - Propafenone—increased plasma concentration of metoprolol and propranolol
- *Antidepressants*:
 - Citalopram, escitalopram, paroxetine—increased metoprolol plasma concentration
 - Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs)
- *Antimalarials: mefloquine*—increased risk of bradycardia
- *Calcium-channel blockers*:
 - Enhanced hypotensive effect
 - Diltiazem—risk of AV block, bradycardia
 - Verapamil—severe hypotension and heart failure
- *Ciclosporin*: increased plasma concentration with carvedilol
- *Clonidine*: increased risk of withdrawal hypertension
- *Diuretics*: enhanced hypotensive effect.
- *Indomethacin and other NSAIDs* antagonize the antihypertensive effects of *b*-blockers.

- *Sympathomimetics* (adrenaline, dobutamine)—increased risk of severe hypertension and bradycardia with non-cardioselective B-blockers

Note: Sotalol, a B-blocker with class III anti-arrhythmic effects, has a number of specific interactions, which should be checked before prescribing.

N.B:

- β -blockers (and other anti-ischaemic drugs) should be withheld for four half-lives (usually about 48 h) when a stress test is planned for the diagnosis and risk stratification of patients with suspected coronary artery disease. β -blockers should be withdrawn gradually to avoid withdrawal effects.
- Nebivolol and bisoprolol are partly secreted by the kidney, whereas carvedilol and metoprolol are metabolized by the liver, hence being safer in patients with renal compromise.
- In diabetic patients, metoprolol appears to slightly worsen diabetes control (HbA1c). This is not the case with carvedilol and nebivolol, which should be the preferred β -blockers in diabetic patients (GEMINI trial).

Calcium channel blockers

Mechanism of action:

CCBs inhibit the inward movement of calcium ions through the slow channels located in the cells of the myocardium, the His–Purkinje system, and in vascular smooth muscle.

The DHP-type CCBs have more affinity for the vascular smooth muscle, resulting in peripheral vasodilatation, reduced blood pressure, and reduced afterload, while the non-DHP type have more effect on the myocardial cells and conduction system, resulting in negative inotropy, myocardial depression, and AV conduction delay.

Classification of CCBs:

- **Dihydropyridine (DHP) type:** nifedipine (The first DHP CCB), amlodipine, felodipine, isradipine, nicardipine, nisoldipine.
- **Non-dihydropyridine (non-DHP) type:** diltiazem and verapamil. Both decrease cardiac inotropism and chronotropism and have a vasodilatory effect. Also, they dilate the coronary arteries. Verapamil has more negative inotropic effect, slightly more AV and SA nodal depressant effect, and stronger vasodilatory effect than diltiazem.

Indications and Clinical evidence:

Table 36-41: Clinical trials of CCBs:

| Trial (date) | Summary |
|--------------|---------|
|--------------|---------|

Chronic coronary syndrome:

CCBs are first line in patients where B-blockers are contraindicated or not tolerated (rate-controlling effects of diltiazem and verapamil may confer an advantage here).

DHP-CCBs may also be used in combination with B-blockers, nitrates, nicorandil, or ivabradine.

| | |
|--|---|
| APSYS (1996) | <i>In patients aged < 70 years with stable angina, both metoprolol and verapamil drugs are well tolerated and that no difference was shown on the effect on mortality, CV endpoints and measures of quality of life.</i> |
| Hypertension: | |
| CCBs are first line for older patients (> 55 years) and black patients. | |
| ALLHAT (2002) | <i>In participants ≥ 55 years with hypertension and at least 1 other CHD risk factor, thiazide-type diuretics are superior to ACEI and CCBs in preventing one or more major forms of CVD in high-risk patients with hypertension and in patients with hypertension and diabetes.</i> |
| VALUE (2003) | <i>In patients ≥ 50 years old with hypertension, either amlodipine and valsartan achieved BP control, but BP was slightly lower in the amlodipine-based group.</i> |
| Syst-Eur (1997) | <i>Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of CV complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major CV endpoints.</i> |
| Atrial fibrillation: | |
| Verapamil may be considered for rate control where firstline options have failed, or are contraindicated or not tolerated. | |

Adverse effects:

- *Bradycardia* (HR < 50 bpm): (non-DHP only) consider dose reduction, exclude heart block. When DHP-CCBs may cause reflex tachycardia.
- *Symptomatic hypotension*: consider dose reduction.
- *Flushing*: dissipates over time—encourage patient to persist with therapy.
- *GI disturbance*: may make constipation worse.
- *Ankle oedema*: often dose related, consider dose reduction or combine with ACE-I or ARB
- *Gingival hyperplasia*: withdraw CCB and consider alternatives.

Contraindications:

- Cardiogenic shock, advanced aortic stenosis, within one month of acute MI, unstable angina or ACS.
- Diltiazem, verapamil—AV block, severe bradycardia, left ventricular failure, sick sinus syndrome, and Wolff Parkinson–White syndrome.

Monitoring:

- Obtain baseline BP and pulse before initiation and after dose changes
- In the absence of side-effects, review within 4 weeks and consider dose titration.
- Headache and flushing are common in the first week or two of treatment and usually resolve over time. Simple analgesics can be used to control headache if necessary. The patient should be reassured and encouraged to continue with therapy.
- Ankle swelling is common, especially with the DHP-type CCB at higher doses (i.e. after increasing from amlodipine 5 mg to 10 mg daily), and may limit the maximum dose.

Drug interactions:

- *Alpha-blockers*: enhanced hypotensive effect
- *Anaesthetics*: enhanced hypotensive effect
- *Anti-arrhythmics*: non-DHP type: increased risk of bradycardia, myocardial depression with amiodarone and risk of asystole when verapamil given with flecainide/disopyramide.
- *Anti-epileptics*: variable effects on plasma levels—consult product literature.
- *Antifungals*
- *Antivirals*
- *Barbiturates*: effect of CCB reduced
- *Beta-blockers*:
 - enhanced hypotensive effect.

- diltiazem—risk of AV block, bradycardia
- verapamil—severe hypotension and heart failure
- *Digoxin*: verapamil increases digoxin levels, with increased risk of AV block/bradycardia
- *Ciclosporin*: variable effects on plasma levels—consult product literature.
- *Ivabradine*: plasma levels increased by diltiazem, verapamil—avoid concomitant use.
- *Statins*: plasma concentration of simvastatin, atorvastatin increased by diltiazem/verapamil—reduce statin dose
- *Sirolimus*: plasma levels increased by diltiazem and verapamil.
- *Tacrolimus*: plasma levels increased by diltiazem and nifedipine
- *Theophylline*: increased plasma levels of theophylline.

Nitrates

Mechanism of action:

Nitrate enters vascular smooth muscle and converted to nitric oxide (NO) leading to activation of cGMP & vasodilation. Nitrate relaxes smooth muscle via dose-dependent dilation of arterial and venous beds to reduce both preload and afterload, and myocardial O₂ demand (reduction in venous return and in LV wall tension).

Classification:

- **Short acting nitrates:** Amyl nitrite (inhalation), Nitroglycerin (trinitrin, GTN), Isosorbide dinitrate.
- **Intermediate-acting nitrates:** Isosorbide dinitrate (oral).
- **Long-acting nitrates:** Isosorbide mononitrate (oral).

Indications & clinical evidence:

- Sublingual GTN is used for the rapid symptomatic relief of angina, either for the relief of acute chest pain or prophylactically to prevent the development of predictable exertional chest pain.
- Oral nitrates should be considered as adjunctive therapy in the prophylaxis of anginal chest pain.
- Intravenous nitrates are used for the management of severe acute chest pain that is unresponsive to sublingual nitrates, and may be used to control blood pressure in acute situations.

Adverse effects:

- *Hypotension:* patients should be advised to sit down before taking sublingual nitrates.
- *Headache:* occurs due to cerebral vasodilatation. Can be reduced by spitting out the sublingual tablet after resolution of chest pain. Concomitant aspirin reduces the occurrence of headaches.

- *Methemoglobinemia* (rare): Metabolism of organic nitrates results in the formation of inorganic nitrites that can oxidize hemoglobin to methemoglobin. Renal dysfunction may be contributing factors. Stop the medication and, when necessary, administering methylene blue.
- *Tolerance*: attenuation or even loss of hemodynamic and anti-ischemic effects during continuous nitrate medication. It is important that physicians should prescribe a 6–10-hour nitrate free interval each day.
- *Rebound* is the abrupt increase in anginal frequency during accidental nitrate withdrawal (e.g., displacement of an intravenous infusion) or during nitrate-free periods.
- *NO[•] resistance* may be defined as de novo hyporesponsiveness to NO[•] effects, whether vascular or antiaggregatory. The occurrence of NO[•] resistance accounts for the finding that some patients with heart failure respond poorly to infused NO[•] donors, irrespective of prior nitrate exposure.
- Worsening of endothelial dysfunction is a potential complication of long-acting nitrates, so the routine use of long-acting nitrates as first line therapy for patients with effort angina needs re-evaluation.

Contraindications:

AS, HCM, Tamponade, Constrictive pericarditis, MS, Cerebral hemorrhage. Concurrent use of PDE-5 inhibitors. RV involvement in AMI (Nitrate-induced fall in LV filling pressure may aggravate hypotension).

Drug interactions

- *Anticoagulants*: infusion of GTN reduces the anticoagulant effect of heparins.
- *Sildenafil, tadalafil, vardenafil*: hypotensive effects of nitrates are significantly enhanced.

Alpha Blockers

Classification:

- **Nonselective α blockers:** Phenoxybenzamine, Phentolamine.
- **Selective α_1 blockers:** Prazosin, Doxazosin, Terazosin.
- **α_{1A} blockers:** Tamsulosin.
- **Selective α_2 blockers:** Yohimbine.

Mechanism of action:

There are two types of alpha-adrenergic receptors: alpha-1 and alpha-2. Alpha-1 adrenergic receptors are located on the vascular smooth muscle (in the skin, sphincters of the gastrointestinal system, kidney, and brain) and cause vasoconstriction when activated by catecholamines such as epinephrine and norepinephrine (NE). The vasoconstriction causes an increase in both systemic arterial blood pressure and peripheral resistance. Alpha-2 adrenergic receptors are located on peripheral nerve endings and inhibit the release of NE when activated; this provides a feedback mechanism for NE to inhibit its release.

Nonselective alpha-adrenergic antagonists cause vasodilation by blocking both alpha-1 and alpha-2 receptors. The blockage of alpha-2 receptors will increase the NE release, which will reduce the force of the vasodilation induced by the blockade of the alpha-1 receptors. These medications work best when there is increased sympathetic activity such as during stress or when there is an increase in circulating catecholamines, making these medications useful for patients with pheochromocytoma.

Selective alpha-1 adrenergic antagonists cause vasodilation by preventing NE from activating the alpha-1 receptor, resulting in a lowering of the blood pressure, allowing alpha-1 blockers to be used for hypertension. Alpha-1 blockers also cause relaxation of smooth muscle in the prostate, which can enable the urine to flow more freely thru the urethra, making the medications useful for the management of benign prostatic hyperplasia (BPH).

Selective alpha-2 adrenergic antagonists inhibit negative feedback of NE, stimulating the sympathetic nervous system. However, there are limited findings on the significance of this mechanism of action in human medicine.

Indications:

- **Nonselective Alpha-blockers** (Phenoxybenzamine and Phentolamine): Both of these medications have FDA approval for use in patients with pheochromocytoma. Phenoxybenzamine is irreversible and phentolamine is reversible alpha-blockers. Both are used intraoperatively to manage hypertensive crisis during pheochromocytoma removal. Phentolamine sees occasional use in the treatment of cocaine-induced cardiovascular complications. In this situation, the use of β -blockers is less desirable due to the risk of unopposed α -adrenergic receptor-mediated coronary vasoconstriction and hypertension. Although it is worth mentioning that it is not a first-line agent for this condition.
- **Selective Alpha-1 Blockers**: Selective alpha-1 blocker ends with the suffix "-osin." These medications include alfuzosin, doxazosin, terazosin, tamsulosin, and prazosin. These medications are FDA approved to treat benign prostatic hyperplasia (BPH). These medications may also be options to treat essential hypertension. However, they are not typically first-line agents for the management of hypertension.
- **Selective Alpha-2 Blockers**: Selective alpha-2 blockers include the medications yohimbine and idazoxan.
- Yohimbine has been used to treat male sexual dysfunction, although the effectiveness has not yet been established and is not currently FDA approved for this use or any other uses. Idazoxan is being used in research, but has no established clinical role has established.

Adverse effects:

Hypotension due to α -1 receptors inhibition, which causes vascular smooth muscle relaxation and vasodilation.

Weakness, tachycardia and tremulousness: occur due to the increased release of norepinephrine when alpha-2 receptors become simultaneously antagonized. This release results in the stimulation of beta receptors due to the spillover of norepinephrine and results in tremulousness and tachycardia.

Adverse systemic effects such as tachycardia and tremulousness are less common with selective alpha-1 blockers.

Cautions:

To best avoid these adverse effects, the patient should take the medication at night.

Caution is necessary when administering alpha-blockers in elderly patients or if previous cataract surgery. These medications can complicate cataract surgery by inducing sudden iris prolapse and pupil constriction during the surgery - also known as "intraoperative floppy iris syndrome."

Lipid lowering drugs

Elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) increase the risk CV disease. This is exacerbated by low high-density lipoprotein cholesterol (HDL-C) and elevated triglycerides.

Lipid lowering drugs include:

1. Statins
2. Fibrates
3. Cholesterol-absorption inhibitors (Ezetimibe)
4. Bile acid binders (resins)
5. Proprotein convertase subtilisin/kexin 9 inhibitors (PCSK-9 inhibitors)
6. Nicotinic acid derivatives.
7. Lomitapide
8. Mipomersen

In terms of lowering CV risk, the wealth of evidence supports the use of statins in the first instance.

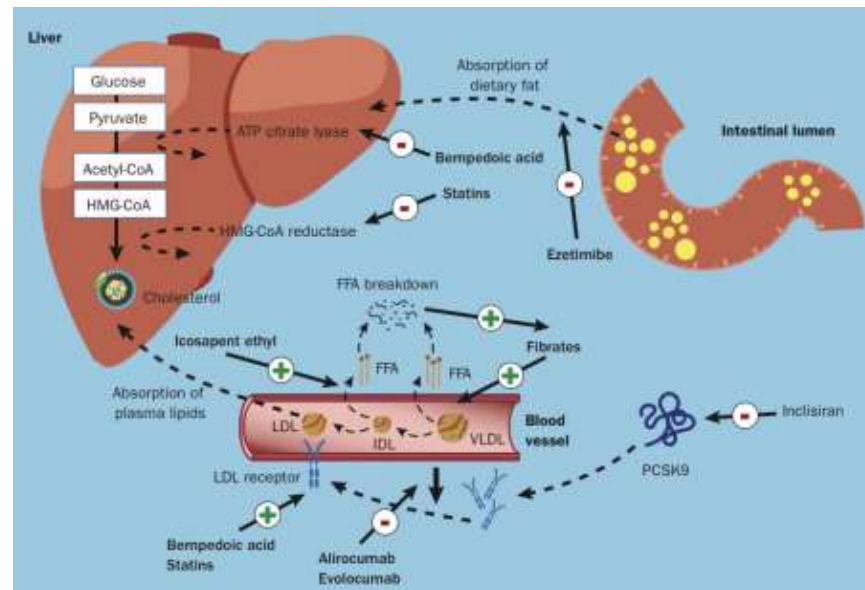


Figure 36-11: Various stages involved in human cholesterol metabolism and how different lipid-lowering therapies interact with these processes to reduce circulating lipid levels. Agents targeting fatty acids generally act to increase their uptake and metabolism, whereas agents targeting cholesterol generally block various metabolic processes. **Source:** Barton AK. Novel approaches to the management of hyperlipidaemia. *Prescriber*. 2023 Oct;34(10):10-6.

| Table 36-42: Impact of lipid lowering drugs on lipid profile: | | | | |
|---|-------------------|----------|----------|---------------|
| Lipid element | Total cholesterol | LDL-C | HDL-C | Triglycerides |
| Statins | ↓ by 30% | ↓ by 40% | ↑ by 6% | ↓ by 20% |
| Fibrates | ↓ by 15% | ↓ by 20% | ↑ by 20% | ↓ by 50% |
| Ezetimibe | ↓ by 15% | ↓ by 20% | ↑ by 3% | ↓ by 8% |

| | | | | |
|-------------------------------|----------|----------|----------|--------------|
| Bile acid sequestrants | ↓ by 10% | ↓ by 25% | | May increase |
| PCSK9 inhibitors | | ↓ by 60% | ↑ 9% | ↓ by 26% |
| Nicotinic acid | | ↓ by 15% | ↑ by 15% | ↓ by 45% |

Statins

(e.g. Atorvastatin, Pravastatin, Rosuvastatin, Simvastatin)

The development of statins began in the mid-1970s, when they were discovered as a fungal metabolite; the first of these being a natural product called mevastatin. Another naturally occurring statin, lovastatin, was soon isolated. Later, lovastatin became the first FDA-approved statin to treat hypercholesterolemia and cardiovascular diseases. Next, two statins were developed based on the structures of these two naturally occurring statins, simvastatin and pravastatin, followed by the newer synthetic varieties (e.g atorvastatin, rosuvastatin).

Mechanism of action:

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting the enzyme Hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, so inhibiting the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. The reduction in intracellular cholesterol promotes increased LDL receptor (LDLR) expression at the surface of the hepatocytes, which in turn results in increased uptake of LDL from the blood, and decreased plasma concentrations of LDL- and other ApoB-containing lipoproteins, including TG-rich particles.

Indications and Clinical evidence:

Table 36-43: Clinical trials of statins:

| Trial (date) | Summary |
|---------------------|----------------|
|---------------------|----------------|

| | |
|---|--|
| Primary prevention: | |
| <ul style="list-style-type: none"> - Anyone with a 10-year cardiovascular risk $\geq 10\%$ (NICE guidelines) - Patients with type 2 DM should now be assessed using QRISK2 like other patients are, to determine whether they should be started on statins. - Patients with type 1 DM who were diagnosed > 10 years ago <u>OR</u> Aged > 40 <u>OR</u> have established nephropathy. | |
| WOSCOPS (1995) | <i>In men, aged 45-64 years, with moderate hypercholesterolemia and no history of MI, pravastatin significantly reduced the incidence of MI and death from CV causes without adversely affecting the risk of death from non CV causes.</i> |
| AFCAPS (1998) | <i>In patients with average TC and LDL-C and below-average HDL-C, lovastatin reduces the risk for the first acute major coronary event.</i> |
| CARDS (2004) | <i>In patients aged 40-75 years with type 2 DM without high LDL-cholesterol, atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first CV disease events.</i> |
| JUPITER (2008) | <i>In apparently healthy participants with LDL-C levels of < 130 mg/dL and high-sensitivity CRP ≥ 2.0 mg/L, rosuvastatin significantly reduced the incidence of MACE.</i> |
| Secondary prevention: | |
| All people with established cardiovascular disease (stroke, TIA, IHD, peripheral arterial disease) | |
| 4S (1994) | <i>In patients with angina pectoris or previous MI and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet, long-term treatment with simvastatin is safe and improves survival.</i> |
| CARE (1996) | <i>In patients with MI who had plasma total cholesterol levels < 240 mg/dL and LDL-C levels of 115-174 mg/dL, Pravastatin lowered the rate of coronary events more among women than among men. The reduction in coronary events was also greater in patients with higher pretreatment levels of LDL cholesterol.</i> |
| LIPID (2000) | <i>In patients who were 31-75 years of age with history of MI or hospitalization for unstable angina and initial plasma total cholesterol levels of 155-271 mg/dL, pravastatin reduced mortality from coronary</i> |

| | |
|---------------------------------|---|
| | <i>heart disease and overall mortality, as compared with placebo, as well as the incidence of all prespecified CV events.</i> |
| HPS (2004) | <i>In participants aged 40-80 years with increased risk of coronary heart disease, simvastatin rapidly reduces the incidence not only of coronary events but also of ischemic strokes, with no apparent effect on cerebral hemorrhage, even among individuals who do not have high cholesterol concentrations.</i> |
| TNT (2005) | <i>In patients with clinically evident CHD and LDL-C < 130 mg/dL, intensive lipid-lowering therapy with atorvastatin (80 mg/day) in patients with stable CHD provides significant clinical benefit beyond that afforded by atorvastatin (10 mg/day). This occurred with a greater incidence of elevated aminotransferase levels.</i> |
| Acute Coronary Syndrome: | |
| MIRACL (2001) | <i>In adults aged 18 years or older with NSTEMI-ACS, lipid-lowering therapy with atorvastatin (80 mg/d) reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization.</i> |
| PROVE-IT (2004) | <i>In patients who had been hospitalized for ACS within the preceding 10 days, intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen.</i> |
| A to Z (2004) | <i>In patients with ACS, receiving of simvastatin 40 mg/d for 1 month followed by 80 mg/d thereafter did not achieve the prespecified end point. However, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of MACE.</i> |

Classification of Statins:

Table 36-44: Statin Dosing and ACC/AHA Classification of Intensity:

| | Low-intensity (LDL-C reduction < 30%) | Moderate-intensity (LDL-C reduction 30-50%) | High-intensity (LDL-C reduction > 50%) |
|--|---|--|--|
|--|---|--|--|

| Lipophilic statins: | | | |
|-----------------------------|-------------|------------------------|-------------|
| Atorvastatin | NA | 10 to 20 mg | 40 to 80 mg |
| Fluvastatin | 20 to 40 mg | 40 mg 2×/day; XL 80 mg | NA |
| Lovastatin | 20 mg | 40 mg | NA |
| Pitavastatin | 1 mg | 2 to 4 mg | NA |
| Simvastatin | 10 mg | 20 to 40 mg | NA |
| Hydrophilic statins: | | | |
| Pravastatin | 10 to 20 mg | 40 to 80 mg | NA |
| Rosuvastatin | NA | 5 to 10 mg | 20 to 40 mg |

Lovastatin and simvastatin are prodrugs, whereas the other statins are administered in their active form.

Their bioavailability is relatively low, owing to a first-pass effect in the liver, and many statins undergo significant hepatic metabolism via CYP450 isoenzymes, except pravastatin, rosuvastatin, and pitavastatin.

Adverse effects:

- *Mild elevation of ALT occurs in 0.5-2.0% of patients on statin treatment, more commonly with potent statins or high doses.* The common definition of clinically relevant ALT elevation has been an increase of three times the ULN on two consecutive occasions.
- *Statin-associated muscle symptoms (SAMS):*
 - *Myalgia:* Statins are associated with muscular pain and tenderness without CK elevation.
 - *Myopathy:* muscle pains in the presence of a raised CK > 5 × ULN (upper limit of normal) indicates myopathy. Statin should be withdrawn and CK rechecked. Low doses of less-potent statins may be cautiously reintroduced with careful monitoring under specialist supervision.

Risks factors for myopathy include advanced age, female sex, low body mass index and presence of multisystem disease such as diabetes mellitus. Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin).

- *Rhabdomyolysis* is the most severe form of statin-induced muscle damage, characterized by severe muscular pain, muscle necrosis, and myoglobinuria potentially leading to renal failure and death. In rhabdomyolysis, CK levels are elevated by ≥ 10 times, and often ≥ 40 times, the ULN.

Increased risk of *new-onset diabetes mellitus*. Patients on statin treatment have been shown to exhibit an increased risk of dysglycemia and development of type 2 diabetes mellitus (T2DM). This effect is probably related to the mechanism of action of statins, as Mendelian randomization studies have confirmed the increased risk of DM in individuals with HMG-CoA reductase polymorphisms that reduce cholesterol synthesis. Nevertheless, the benefits in terms of CV event reduction greatly exceed the risks of statin therapy.

- Increased frequency of *proteinuria* has been reported for all statins, but has been analysed in more detail for rosuvastatin.
- There is some evidence that statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. This effect is not seen in primary prevention. For this reason, the Royal College of Physicians recommend avoiding statins in patients with history of intracerebral haemorrhage.
- *GI disturbance*: advise patient to take with or after food—ideally with their evening meal rather than last thing at night.
- *Insomnia*:
 - try taking the dose earlier in the day, for example with the evening meal or earlier if necessary
 - try an alternative statin if the problem persists.

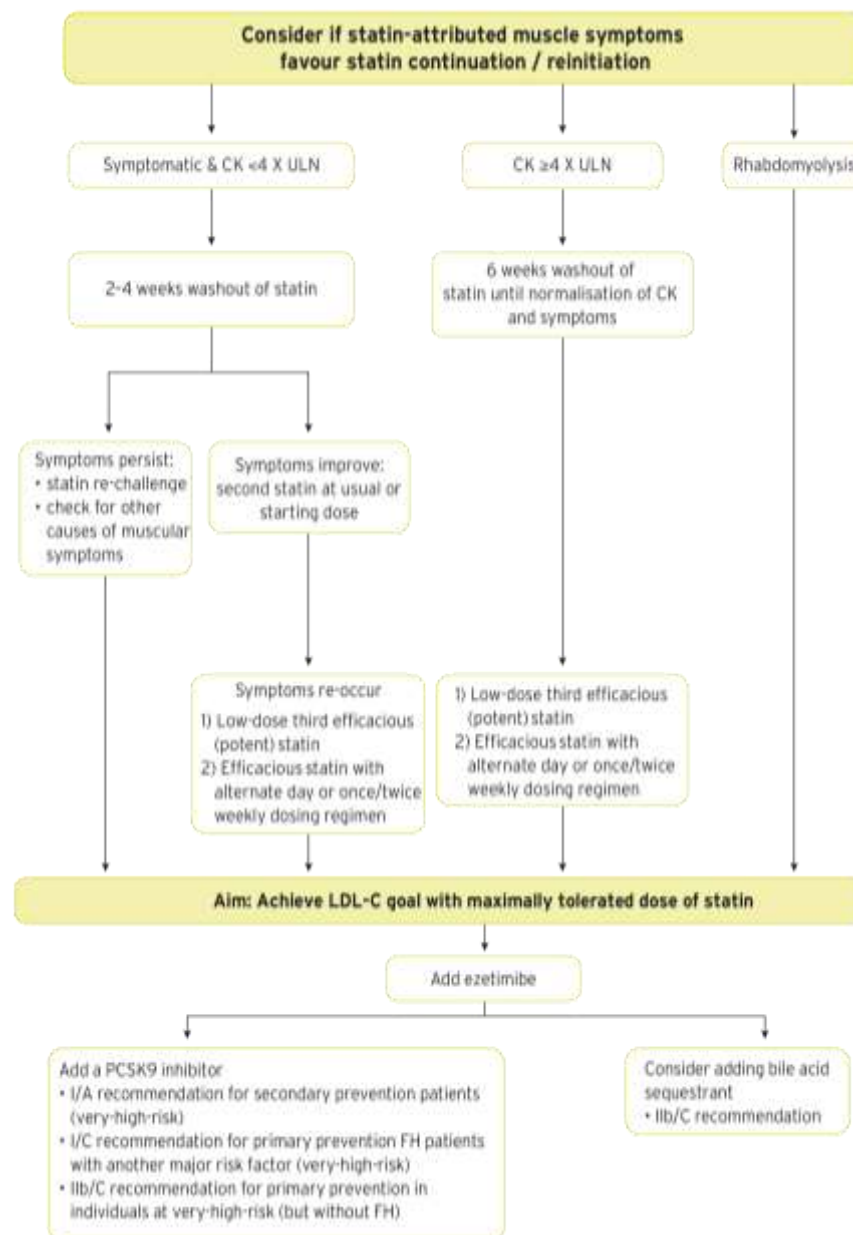


Figure 36-12: Algorithm for the treatment of muscular symptoms during statin treatment. Source: 2019 ESC/EAS Guidelines for the management of dyslipidaemias.

Adherence issues:

- 50% of patients stop taking statin therapy within one year of initiation and 75% within three years.
- It is essential that patients understand the need for statin therapy to reduce their long-term risk of CV events, and that once initiated statins should be continued long term.
- Care should be taken to address adverse effects should they occur, in order to facilitate ongoing adherence.

In patients failing to respond to statin therapy, compliance issues should be suspected in the first instance and all efforts made to resolve these before switching to an alternative statin.

Contraindications:

- Hypersensitivity to the individual statin
- Active liver disease (aspartate transaminase (AST) or alanine aminotransferase (ALT) level >100 iu/L) or unexplained persistent isolated elevations of serum transaminases
- Pregnancy and lactation

Cautions:

- Hypothyroidism should be corrected before initiation of a statin.
- Patients with a high alcohol intake
- Patients with risk factors for myopathy or rhabdomyolysis
- Acute porphyria (rosuvastatin is thought to be safe)
- Renal disease—dose reductions may be necessary.
- Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins.

Drug interactions:

Interaction of statins with concomitant drug therapy is considered a risk factor for myopathy.

For example, combination of statins with gemfibrozil (one of the fibrates) enhances the risk of myopathy, and its association with statins must be avoided. Note that, there is no or very little increased risk for myopathy when combining statins with other fibrates, such as fenofibrate, bezafibrate, or ciprofibrate.

Table 36-45: Drugs potentially interacting with statins metabolized by cytochrome P450 3A4 leading to increased risk of myopathy and rhabdomyolysis:

| Anti-infective agents | Calcium antagonists | Other |
|-------------------------|---------------------|-------------|
| Itraconazole | Verapamil | Ciclosporin |
| Ketoconazole | Diltiazem | Danazol |
| Posaconazole | Amlodipine | Amiodarone |
| Erythromycin | Ranolazine | |
| Clarithromycin | Grapefruit juice | |
| Telithromycin | Nefazodone | |
| HIV protease inhibitors | Gemfibrozil | |

- *Anti-arrhythmics*: increased risk of myopathy when simvastatin given with amiodarone; maximum simvastatin dose = 20 mg
- *Antibacterials*:
 - Macrolides (e.g. erythromycin, clarithromycin) are an important interaction. Statins should be stopped until patients complete the course:

- ✓ clarithromycin—increases plasma concentrations of pravastatin and atorvastatin.
- ✓ clarithromycin, erythromycin, telithromycin—increase the risk of myopathy with simvastatin.
- daptomycin—increased risk of myopathy with statins
- fusidic acid—increased risk of myopathy with simvastatin
- telithromycin—increased risk of myopathy with atorvastatin; avoid concurrent use.
- *Anticoagulants*: caution with use of warfarin and other coumarins with atorvastatin, simvastatin, fluvastatin, rosuvastatin
- *Antifungals*:
 - itraconazole, ketoconazole, posaconazole, miconazole—increased risk of myopathy with simvastatin; avoid concomitant use.
 - itraconazole, posaconazole—increase risk of myopathy with atorvastatin; avoid concomitant use
- *Antivirals*: use under specialist supervision only
- *Calcium-channel blockers*:
 - diltiazem, verapamil—possible increased risk of myopathy with simvastatin; dose reduction required.
 - diltiazem—increases plasma concentration of atorvastatin.
- *Ciclosporin*: increased risk of myopathy with statins; dose reductions required; avoid concomitant use with rosuvastatin.
- *Colchicine*: increased risk of myopathy with statins
- *Danazol*: possible increase in myopathy with simvastatin
- *Fibrates*: avoid concomitant use of statins with gemfibrozil; increased risk of myopathy when other fibrates are used with statins. (Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to marked increases in plasma concentrations of statins).
- *Grapefruit juice*: plasma concentrations of simvastatin increased—avoid concomitant use; possible increase in plasma concentrations of atorvastatin with excessive intake.
- *Nicotinic acid*: increased risk of myopathy with statins.

Table 36-46: Summary of recommendations for monitoring lipids and enzymes in patients, before and on lipid-lowering therapy:

Testing lipids:

How often should lipids be tested?

- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1-12 weeks, with the exception of conditions where prompt drug treatment is suggested, such as ACS and very high-risk patients.

How often should a patient's lipids be tested after starting lipid-lowering treatment?

- After starting treatment: 8 (\pm 4) weeks.
- After adjustment of treatment: 8 (\pm 4) weeks until the goal is achieved.

How often should lipids be tested once a patient has achieved the target or optimal lipid level?

- Annually (unless there are adherence problems or other specific reasons for more frequent reviews).

Monitoring liver and muscle enzymes:

How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?

- Before treatment.
- Once, 8-12 weeks after starting a drug treatment or after dose increase.
- Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

• If ALT < 3 ULN:

- Continue therapy.
- Recheck liver enzymes in 46 weeks.

• **If ALT rises to ≥ 3 ULN:**

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 46 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

How often should CK be measured in patients taking lipid-lowering drugs?

• **Pre-treatment:**

- Before starting therapy.
- If baseline CK is > 4 ULN, do not start drug therapy; recheck.

• **Monitoring:**

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk, such as: elderly patients, those on concomitant interfering therapy, multiple medications, liver or renal disease, or athletes.

What if CK becomes elevated in a person taking lipid-lowering drugs?

Re-evaluate indication for statin treatment.

• **If ≥ 4 ULN:**

- If CK >10 ULN: stop treatment, check renal function, and monitor CK every 2 weeks.
- If CK <10 ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK between 2 and 6 weeks.
- If CK <10 ULN: if symptoms present, stop statin and monitor normalization of CK, before rechallenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

• **If < 4 ULN:**

- *If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).*
- *If muscle symptoms, monitor symptoms and CK regularly.*
- *If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin.*
- *Consider rechallenge with the same or another statin.*

Consider low-dose statin, alternate day or once/twice weekly dosing regimen, or combination therapy.

In which patients should HbA1c or blood glucose be checked?

- *Regular checks of HbA1c or glucose should be considered in patients at high-risk of developing diabetes, and on high-dose statin treatment.*
- *Groups to be considered for glucose control are the elderly and patients with metabolic syndrome, obesity, or other signs of insulin resistance.*

Pleiotropic properties of statins:

Statins also exert therapeutic actions through mechanisms independent of their cholesterol-lowering capacity. HMG-CoA reductase is responsible for the conversion of HMG-CoA to mevalonate, which is a crucial intermediate molecule in the production of cholesterol and a wide range of isoprenoid intermediates. These intermediate compounds are required for the post-translational modification and activation of many key proteins, involved in numerous important intracellular signaling pathways. These pleiotropic effects are diverse in nature and include the improvement of cardiovascular function, broad antioxidant and anti-inflammatory effects, anti-fibrotic effects, enhancement of bone formation, and neuro- and renal-protective effects. Statins decrease the expression of anti-apoptotic proteins and increase the expression of pro-apoptotic proteins that activate caspases and trigger intrinsic apoptosis. In addition, statins may inhibit EMT -the necessary step for cancer metastasis-.

Fibrates

(Bezafibrate, Ciprofibrate, Fenofibrate, Gemfibrozil, Pemafibrate)

Mechanism of action:

Fibrates are agonists of peroxisome proliferator-activated receptors (PPAR- α), acting via transcription factors regulating, among other things, various steps in lipid and lipoprotein metabolism. As a consequence, fibrates have good efficacy in lowering fasting TG levels, as well as post-prandial TGs and TG-rich lipoprotein (TRL) remnant particles.

Indications and Clinical evidence:

Table 36-47: Clinical trials of Fibrates:

| Trial (date) | Summary |
|----------------------|---|
| | While fibrates may seem an obvious choice for the treatment of a patient with diabetes where raised triglycerides are often a problem, statins remain the first-line choice even for this group, due to the overwhelming trial evidence of benefit. Combination use of statins plus fibrates may be considered in patients requiring lipid lowering beyond monotherapy. However, the combination does increase the risk of myopathy and possibly rhabdomyolysis, and needs careful monitoring. The clinical effects of fibrates have been illustrated by 6 RCTs: the Helsinki Heart Study (HHS), Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT), Bezafibrate Infarction Prevention (BIP), Lower Extremity Arterial Disease Event Reduction (LEADER), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials. |
| HHS (1987) | <i>In asymptomatic middle-aged men with primary dyslipidemia (non-HDL cholesterol ≥ 200/dL in two consecutive pretreatment measurements), gemfibrozil caused a marked increase in HDL-C and persistent reductions in levels of total, LDL, and non-HDL cholesterol and triglycerides.</i> |
| VA-HIT (1999) | <i>In men with coronary heart disease, an HDL-C ≤ 40 mg/dL, and LDL-C ≤ 140 mg/dL, gemfibrozil resulted in a significant reduction in the risk of MACE in patients with coronary disease whose primary lipid abnormality was</i> |

| | |
|----------------------|---|
| | <i>a low HDL-C level. The findings suggest that the rate of coronary events is reduced by raising HDL-C and lowering of triglycerides without lowering LDL-C levels.</i> |
| BIP (2009) | <i>In patients aged 45-74 years with a history of MI and/or angina and (Total cholesterol 180-250 mg/dl, triglyceride < 300 mg/dl, LDL-C < 180 mg/dl, and HDL-cholesterol < 45 mg/dl), HDL-C level-raising therapy with bezafibrate is associated with long-term mortality reduction that may be related to the degree of HDL-C response to treatment.</i> |
| LEADER (2001) | <i>In men with lower extremity arterial disease, bezafibrate has no effect on the incidence of coronary heart disease and of stroke combined but may reduce the incidence of non-fatal coronary events, particularly in those aged < 65 years at entry.</i> |
| FIELD (2005) | <i>In patients with type 2 DM with no indication for lipid-lowering therapy, fenofibrate was not associated with a difference in the primary composite endpoint of CHD death or nonfatal MI compared with placebo at 5-year follow-up.</i> |

Adverse effects:

- Key adverse effects include GI disturbances, which are usually self-limiting.
- Fibrates, when used in renal failure or in combination with statins, are associated with an increased risk of myositis of 1%. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to marked increases in plasma concentrations of statins. As fenofibrate does not share the same pharmacokinetic pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy.
- Fibrates raise serum creatinine level. This increase seems to be fully reversible when the drug is stopped. Data from meta-analyses suggest that a reduction of calculated GFR does not reflect any adverse effects on kidney function.
- Fibrates are associated with a slightly increased risk of pancreatitis.

N.B:

- Fibrates have been reported to raise serum homocysteine levels. The increase in homocysteine levels caused by fibrates has been considered to be relatively neutral with respect to CVD risk. However, a fibrate-induced increase in homocysteine may blunt elevation of both HDL-C and ApoA1 levels, and this effect may contribute to the smaller than estimated benefits of fenofibrate in CV outcome parameters.
- Pemafibrate is a new selective peroxisome proliferator-activated receptor- α modulator with a superior benefit-risk balance compared with conventional fibrates.

Contraindications:

- Known hypersensitivity.
- Severe renal impairment, including those with end-stage renal disease and those receiving dialysis.
- Active liver disease.
- Gallbladder disease.
- Nursing mothers.

Cautions:

- Paradoxical decreases in HDL cholesterol (HDL-C) level reported.
- Rule out secondary causes of hyperlipidemia before initiating therapy.
- Withdraw therapy if no adequate response seen after 2-3 months.

Drug interactions:

- *Antibacterials*: increased risk of myopathy with daptomycin
- *Anticoagulants*: enhance effect of warfarin and other coumarins
- *Antidiabetic drugs*:
 - *rosiglitazone* levels increased by gemfibrozil—consider reducing rosiglitazone dose.
 - increased risk of severe hypoglycaemia when gemfibrozil is given with repaglinide.

○ *Lipid-lowering drugs:*

- increased risk of cholelithiasis and gall bladder disease when fibrates are used with ezetimibe—discontinue if suspected.
- *increased* risk of myopathy when fibrates are used with statin.
- avoid *concomitant* use of gemfibrozil and statins except under specialist supervision.

Ezetimibe

Mechanism of action:

Ezetimibe acts by interfering with the transportation of cholesterol across the brush-border in the GI tract [by interacting with the Niemann-Pick C1-like protein 1 (NPC1L1)] without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption, ezetimibe reduces the amount of cholesterol delivered to the liver. Therefore, the liver reacts by upregulating LDLR expression, which in turn leads to increased clearance of LDL from the blood.

Ezetimibe is rapidly absorbed and extensively metabolized to pharmacologically active ezetimibe glucuronide. The primary effect of ezetimibe on the lipid profile is a significant reduction in LDL, which is accompanied by a small reduction in triglyceride and an increase in HDL levels.

Indications and Clinical evidence:

Table 36-48: Clinical trials of Ezetimibe:

| Trial (date) | Summary |
|-------------------------|--|
| | Ezetimibe should be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose, or in cases where a statin cannot be prescribed. The usual dose of ezetimibe is 10 mg once daily can be administered in the morning or evening irrespective of food intake. |
| SEAS (2008) | <i>In patients with mild-to-moderate, asymptomatic aortic stenosis, simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis.</i> |
| SHARP (2011) | <i>In patients with advanced CKD, reduction of LDL-C with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events.</i> |

**IMPROVE-IT
(2015)**

In patients who had been hospitalized for ACS within the preceding 10 days and had LDL-C levels of 50-100 mg/dL (if they were receiving lipid-lowering therapy) or 50-125 mg/dL (if they were not receiving lipid-lowering therapy), The combination of simvastatin and ezetimibe achieved LDL of 53 mg/dl (versus 69 mg/dl with simvastatin only), which translated into a 10% reduction of MI, and 20% reduction of stroke. Moreover, lowering LDL-C to levels below previous targets provided additional benefit.

Adverse effects:

- Key adverse effects include GI disturbances, headache, and fatigue.
- Myalgia can occur during therapy .. check CK to exclude myopathy.
- Hypersensitivity reactions including rash, angioedema, and anaphylaxis have been reported.

Drug interactions:

- *Ciclosporin*: plasma concentrations of both drugs may be increased.
- *Lipid-lowering drugs*: increased risk of myopathy and rhabdomyolysis when added to statins.

Bile acid sequestrants (resins)
(Colestyramine, Colestipol, and Colesevelam)

Mechanism of action:

Bile acids are synthesized in the liver from cholesterol and are released into the intestinal lumen, but most of the bile acid is returned to the liver from the terminal ileum via active absorption.

Bile acid sequestrants are not systemically absorbed or altered by digestive enzymes, so they bind the bile acids and prevent the reabsorption of both the drug and cholesterol into the blood, and thereby remove a large portion of the bile acids from the enterohepatic circulation. The liver, depleted of bile, synthesizes more from hepatic cholesterol, therefore increasing the hepatic demand for cholesterol and increasing LDLR expression, which results in a decrease of circulating LDL.

The primary effect of bile acid sequestrants is therefore a reduction in LDL cholesterol levels, but the drugs can increase triglyceride levels, exacerbating hypertriglyceridaemia.

Indications and Clinical evidence:

Table 36-49: Clinical trials of Cholestyramine:

| Trial (date) | Summary |
|------------------------|--|
| | Bile acid sequestrants have contributed greatly to the demonstration of the efficacy of LDL-C lowering in reducing CV events in hypercholesterolemic people, with a benefit proportional to the degree of LDL-C lowering. Of note, these studies were performed before many of the modern treatment options. |
| LRC-CPPT (1984) | <i>In asymptomatic men with primary hypercholesterolemia (type II hyperlipoproteinemia), the cholestyramine group experienced a 24% reduction in definite coronary heart disease death and a 19% reduction in nonfatal MI.</i> |

Adverse effects:

GI adverse effects (including constipation, diarrhea, nausea, vomiting, and bloating) even at low doses

Contraindications:

- Hypersensitivity to bile-sequestering resins
- Complete biliary obstruction

Cautions:

These agents raise TG. Not for use with baseline fasting triglyceride levels ≥ 300 mg/dL or type III hyperlipoproteinemia; use with caution in patients with triglyceride levels 250-299 mg/dL.

Perform fasting lipid panel in 4-6 weeks after initiation; discontinue use if triglycerides are > 400 mg/dL.

Drug interactions ⁽¹⁾:

- *Anticoagulants*: cholestyramine may increase or reduce the efficacy of warfarin and other coumarins.
- Bile acid sequestrants may affect the absorption of other drug therapies, including digoxin, thyroid hormones, fat-soluble vitamins (A, D, and K), and thiazide diuretics.
- As a result, other drug therapies should be taken at least 1 hour before or 4 hours after bile acid sequestrants, to reduce possible interference with absorption.

(1) Colesevelam is better tolerated and has fewer interactions with other drugs, and can be taken with statins and other drugs.

Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors

(Alirocumab, Evolocumab and Inclisiran)

When PCSK9 protein binds to LDL receptors (LDLR), it reduces LDLR expression by promoting LDLR lysosomal catabolism which results in a subsequent increase in plasma LDL concentrations. On the contrary, the lower concentration or function of PCSK9 is related to lower plasma LDL-C levels.

PCSK9 inhibitors include two types: **(1)** Monoclonal antibodies that reduce the plasma level of PCSK9. It includes alirocumab and evolocumab. **(2)** Small interfering RNA (siRNA) that prevents hepatic synthesis of PCSK9. Inclisiran is a first-in-class.

Mechanism of action:

(3) Anti-PCSK9 Monoclonal Antibodies:

Alirocumab and Evolocumab are monoclonal antibodies (mAbs) that reduce the plasma level of PCSK9, which result in increased expression of LDLRs at the cell surface and therefore in a reduction of circulating LDL-C levels. Statin treatment increases circulating PCSK9 serum levels, and thus the best effect of these mAbs has been demonstrated in combination with statins.

(4) Small interfering RNA (Inclisiran):

Inclisiran is a long-acting, subcutaneously administered small interfering or 'silencing' RNA (siRNA)-based therapeutic oligonucleotide, specifically inhibits synthesis of PCSK9 in the liver, leading to increased hepatic uptake of circulating LDL-C and, hence, lowered plasma LDL-C levels.

Indications and Clinical evidence:

Table 36-50: Clinical trials of PCSK9 inhibitors:

| Trial (date) | Summary |
|--|---------|
| Anti-PCSK9 Monoclonal Antibodies: | |

They have been approved in 2 groups of patients:

- Patients with established CV disease whose LDL remains > 70 mg/dl with statin (FOURIER and ODYSSEY OUTCOMES trials). CV events are reduced by ~15%, but the benefit is more striking in patients whose baseline LDL is > 100 mg/dl or those who do not tolerate any statin (risk reduction > 25%).
- Patients with familial hypercholesterolemia whose LDL remains > 100 mg/dl with statin therapy.

| | |
|---------------------------|---|
| FOURIER (2017) | <i>In patients with atherosclerotic CVD, and LDL-C levels \geq 70 mg/dL who were receiving statin therapy, evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg/dL and reduced the risk of CV events.</i> |
| ODYSSEY (2018) | <i>In patients after hospitalization for acute MI or unstable angina, treated with statins, and with LDL-C \geq 70 mg/dL, non-HDL cholesterol \geq 100 mg/dL, or ApoB \geq 80 mg/dL, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo.</i> |

Small interfering RNA (Inclisiran):

Pooled meta-analysis of 3 studies (ORION-9, -10, and -11), inclisiran led to an LDL-C reduction of ~50% with a substantial number of patients achieving pre-specified LDL-C thresholds of < 100 mg/dl, < 70 mg/dl, and < 50 mg/dl (80.2%, 67.9%, and 51.8%, respectively) after 1.5 years of follow-up.

Adverse effects:

Itching at the site of injection and flu-like symptoms.

Dosing Considerations

Alirocumab: 300 mg SC q4Weeks initially, may adjust dose by 150 mg SC q2Weeks.

Evolocumab: 420 mg SC once monthly

LDL-lowering effects may be measured as early as 4 weeks after initiation. Note that LDL-C can vary during dosing interval in some patients; recommend measuring LDL-C just before next scheduled dose.

Inclisiran: 300 mg administered as a single SC injection on day 1, day 90 and every 6 months thereafter.

Drug interactions:

No interaction with oral drugs, as they will not interfere with pharmacokinetics or pharmacodynamics.

n-3 fatty acids
(Omega-3)

Mechanism of action:

The n-3 (or omega-3) fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] can be used at pharmacological doses to lower TGs. n-3 fatty acids (2-4 g/day) affect serum lipids and lipo-proteins, in particular VLDL concentrations. The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to decreased secretion of ApoB.

Indications and Clinical evidence:

| Table 36-51: Clinical trials of n-3 fatty acids: | |
|--|---------|
| Trial (date) | Summary |
| n-3 fatty acids reduce TGs by ~30–40%, but their effects on other lipoproteins are trivial. A Cochrane meta-analysis from 79 trials reported no overall effect of omega-3 PUFAs on total mortality. This may be due to the low dose of omega-3 used in those trials and to the fact that these formulations contain both EPA and DHA acids (DHA is less likely to be beneficial). Depending on the formulation, 1 gram of fish oil only contains ~350–800 mg of omega-3 fatty acids; ≥ 1 gram of omega-3 (>> 1 gram of fish oil) is likely required for benefit. | |

| | |
|-----------------------------|---|
| EVOLVE II (2018) | <i>In Adult patients with severe hypertriglyceridemia , an intermediate dose of Omega-3 carboxylic acids (2 g daily) significantly lowers TG and non-HDL cholesterol concentrations. It may benefit individuals at risk of acute pancreatitis and cardiovascular disease.</i> |
| ASCEND (2018) | <i>Among patients with DM without evidence of CV disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n-3 fatty acid supplementation and those who were assigned to receive placebo.</i> |
| REDUCE-IT (2019) | <i>Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo.</i> |

Adverse effects:

- The most common side effect is GI disturbance.
- The antithrombotic effects may increase the propensity for bleeding, especially if given in addition to aspirin/clopidogrel.
- Data from one study have associated a risk of prostate cancer with high dietary intake of n-3 PUFAs.

Nicotinic acid (Niacin, Vitamin B3)

Mechanism of action:

Nicotinic acid has key action sites in both the liver and adipose tissue.

In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 resulting in decreased secretion of VLDL particles, which is also reflected in reductions of plasma levels of both IDL and LDL particles. Nicotinic acid primarily raises HDL-C and ApoA1 by stimulating ApoA1 production in the liver.

In the adipose tissue, Niacin reduces fat degradation which reduces the release of free fatty acids in the circulation, reducing VLDL synthesis.

Indications and Clinical evidence:

Table 36-52: Clinical trials of Nicotinic acid:

| Trial (date) | Summary |
|----------------------------|--|
| | Niacin was the first lipid-lowering drug to show a reduction in MI and total mortality in the Coronary Drug Project (secondary prevention trial of patients with prior MI). Nicotinic acid is poorly tolerated with a high incidence of facial flushing, which results in frequent treatment discontinuation. As a result, nicotinic acid has failed to deliver the outcomes demonstrated in the Coronary Drug Project in wider clinical practice. |
| AIM HIGH (2011) | <i>Among patients with atherosclerotic CV disease and LDL-C < 70 mg/dl, there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.</i> |

Adverse effects:

Common adverse effects include GI disturbance (nausea, vomiting diarrhea, dyspepsia, abdominal pain), flushing, and rash.

Strategies to minimize flushing with nicotinic acid:

- Start at a low dose and increase slowly in line with the dose titration schedule.
- Delay dose increases if necessary in patients experiencing significant flushing.
- Avoid drinking alcohol and hot drinks at the same time as taking the dose of nicotinic acid, as these will exacerbate the flushing side-effects.
- Consider the use of aspirin or a NSAID, which can reduce the severity of flushing: a single dose of aspirin 600 mg or ibuprofen 400 mg half an hour before taking the nicotinic acid dose is recommended.

Contraindications:

- Hypersensitivity
- Hepatic disease, active peptic ulcer, severe hypotension, arterial bleeding

Drug interactions:

- Lipid-lowering drugs: increased risk of myopathy when nicotinic acid is combined with statins.

Lomitapide

The microsomal TG transfer protein (MTP) transfers TGs and phospholipids from the endoplasmic reticulum to ApoB, as a necessary step in the formation of VLDL. MTP inhibition thus prevents the formation of VLDL in the liver and of chylomicrons in the intestine. Lomitapide is an MTP inhibitor designed for o.d. oral treatment of HoFH.

As a consequence of its mechanism of action, lomitapide has been shown to be associated with increased aminotransferase levels, which most likely reflects the increased fat in the liver, as well as poor GI tolerability. The GI side effects were the most frequent reasons preventing a further increase in the dose of lomitapide in clinical trials. However, it has been noted that the frequency and intensity of GI side effects generally decrease with time. Therefore, prescription of lomitapide requires careful patient education and liver function monitoring during therapy.

Mipomersen

Mipomersen is an antisense oligonucleotide able to bind the mRNA of ApoB-100, which triggers the selective degradation of mRNA molecules. After SC injection, the oligonucleotide is preferentially transported to the liver, where it binds to a specific mRNA preventing the translation of ApoB protein and, consequently, reducing the production of atherogenic lipids and lipoproteins, including LDL and Lp(a).

An adjunct to lipid-lowering medications and diet, mipomersen is indicated to reduce LDL-C in patients with HoFH. Mipomersen is currently approved by the US FDA, but not by the European Medicines Agency (EMA).

Reactions at the injection site are the most common adverse effects observed in patients treated with mipomersen. However, the main concerns regarding mipomersen's safety are related to liver toxicity. The efficacy and safety of long-term mipomersen treatment are currently under evaluation in patients with severe HeFH, and in statin-'intolerant' patients.

ATP citrate lyase inhibitor

(Bempedoic acid)

Mechanism of action:

Bempedoic acid is a pro-drug that inhibits cholesterol synthesis by inhibiting the action of ATP citrate lyase, a cytosolic enzyme upstream of HMG-coA reductase.

Indications and Clinical evidence:

Table 36-53: Clinical trials of Bempedoic acid:

| Trial (date) | Summary |
|---------------------|--|
| | Bempedoic acid monotherapy lowered LDL-C in patients not taking a statin by about 30%. Bempedoic acid + ezetimibe lowered LDL-C in patients not on statins by 50%. |
| CLEAR (2023) | <i>Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events.</i> |

Adverse effects:

- Elevations in the hepatic-enzyme level and renal events.
- Hyperuricemia, gout and cholelithiasis.

Glucose lowering drugs

Therapeutic agents that manage hyperglycaemia can be broadly characterized as one of five groups:

- 6) Insulin providers (insulin, sulfonylureas, and meglitinides);
- 7) Insulin sensitizers (metformin and pioglitazone);
- 8) Incretin ⁽¹⁾-based therapies (GLP1-RAs and DPP4 inhibitors);
- 9) Gastrointestinal glucose absorption inhibitor (acarbose); and

(1) *Incretins are gut peptides that are secreted after nutrient intake and augment the secretion of insulin from pancreatic beta cells of the islets of Langerhans by a blood-glucose-dependent mechanism.*

10) Renal glucose reuptake inhibitors (SGLT2 inhibitors).

Noninsulin medications vary considerably with respect to efficacy and safety. Most noninsulin medications result in similar HbA1c lowering, with meta-analysis data indicating that, in general, any second-line, noninsulin medication will lower A1c by approximately 0.7% to 1% when added to metformin. However, the DPP-4 inhibitors and SGLT-2 inhibitors tend to result in less HbA1c lowering than the other classes.

Table 36-54: Main drugs used in the management of diabetes mellitus:

| Mechanism of action | Side-effects | Notes |
|---|--|---|
| Insulin: | | |
| Direct replacement for endogenous insulin | -Hypoglycaemia -Weight gain -Lipodystrophy | Can be classified according to source (analogue, human sequence and porcine) and duration of action (short, immediate, long-acting) |
| Biguanides (Metformin) | | |
| Cellular mechanism: Activate AMP kinase, modulation of respiratory-chain complex 1 Physiologic actions: <ul style="list-style-type: none"> - ↑ insulin sensitivity - ↓ hepatic gluconeogenesis - ↓ absorption of carbohydrates | -GI upset (diarrhea) -Lactic acidosis | - First-line drug in the management of T2DM - Does not cause hypoglycemia or weight gain - Cannot be used if eGFR of < 30 ml/min - Stop during episodes of tissue hypoxia (e.g MI) - Stop before IV contrast (e.g Angiography) and 2 days before general anaesthesia - Metformin reduces intestinal absorption of vit B12 and may lower serum B12 concentration. |
| Sulfonylurea: (e.g gliclazide and glimepiride) | | |
| Cellular mechanism: | - Hypoglycaemia - Weight gain | - Avoid in breast feeding and pregnancy |

| | | |
|--|--|--|
| <p>Close KATP channels ↑ Insulin secretion on beta-cell plasma membranes</p> <p>Physiologic actions:</p> <p>Stimulate pancreatic beta cells to secrete insulin</p> | <p>- Hyponatraemia (due to SIADH)</p> | |
| <p>Thiazolidinediones: (pioglitazone, Rosiglitazone)</p> | | |
| <p>Cellular mechanism:</p> <p>Activate the nuclear transcription factor PPAR-γ</p> <p>Physiologic actions:</p> <p>Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake</p> | <p>- Weight gain</p> <p>- Fluid retention</p> <p>- ↑risk of fracture</p> | <p>- Contraindicated in patients with a history of bladder cancer and congestive heart failure.</p> <p>- In patients who fail to show adequate response to pioglitazone, stop it</p> |
| <p>Sodium-glucose co-transporter 2 (SGLT-2) inhibitors:</p> | | |
| <p>Cellular mechanism:</p> <p>Inhibit SGLT-2 in the proximal nephron</p> <p>Physiologic actions:</p> <p>Inhibits reabsorption of glucose in the proximal tubules</p> | <p>- Urinary tract infection</p> | <p>- Typically result in weight loss</p> <p>- Low incidence of hypoglycemia</p> |
| <p>DPP-4 inhibitors: (-gliptins)</p> | | |

| | | |
|---|--|---|
| <p>Cellular mechanism: Inhibit DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations</p> <p>Physiologic actions: Increases incretin levels (by inhibiting its breakdown) which inhibit glucagon secretion and increase insulin secretion</p> | <p>- Well tolerated but ↑ risk of pancreatitis</p> | <p>- Weight neutral</p> <p>- DPP-4 inhibitors require dose adjustment in patients with moderate or severe renal impairment (except Linagliptin)</p> |
| <p>Glucagon-like peptide (GLP-1) agonists: (-tides)</p> | | |
| <p>Cellular mechanism: Activate GLP-1 receptors</p> <p>Physiologic actions: Incretin mimetic which inhibits glucagon secretion and increase insulin secretion</p> | <p>- Nausea and vomiting</p> <p>- Pancreatitis</p> | <p>Typically result in weight loss</p> <p>Stop exenatide if pancreatitis is diagnosed</p> |
| <p>Meglitinides: (e.g. repaglinide, nateglinide)</p> | | |
| <p>Like sulfonylureas, increase pancreatic insulin secretion as they bind to an ATP-dependent K⁺ channel on the cell membrane of pancreatic beta cells</p> | <p>- Weight gain</p> <p>- Hypoglycaemia</p> | <p>often used for patients with an erratic lifestyle</p> |

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

Mechanism of action:

GLP-1 RAs mimic the effects of native GLP-1, which increases insulin secretion, inhibits glucagon secretion, increases satiety and slows gastric emptying. Notably, the insulinotropic and glucagonostatic effects are glucose dependent, and therefore the risk of hypoglycemia is very low. Furthermore, during hypoglycemia treatment with a GLP-1 RA does not, for unexplained reasons, impair the glucagon response or the general hypoglycemic counter-regulation.

Classification:

- **Short acting** [few hours daily]: this group comprises lixisenatide OD and exenatide BID.
- **Long-acting**: including liraglutide OD, and dulaglutide, semaglutide, exenatide and efpeglanitide with weekly (OW) administration. Semaglutide has also been developed as a tablet for daily administration, but when absorbed into the blood it has the half-life of the injectable semaglutide once weekly.

With respect to reduction in HbA1c and body weight, the most effective GLP-1 RA is semaglutide SC OW or oral OD both; followed by liraglutide 1.8 mg OD and dulaglutide 1.5 mg OW.

Indications and Clinical evidence:

Table 36-55: Clinical trials of GLP-1 RAs:

| Trial (date) | Summary |
|---------------------|---|
| | THE ADA guidelines suggest treatment with GLP-1RA in patients with type 2 DM and: (i) established CVD <u>or</u> (ii) without established CVD but with high-risk indicators including age > 55 years, carotid and/or lower extremity or coronary artery stenosis > 50%, LVH, eGFR < 60 ml/min independently of baseline HbA1c. |
| ELIXA (2015) | <i>In patients with type 2 diabetes who had had a recent ACS within the previous 180 days, the addition of lixisenatide to usual care did not significantly alter the rate of MACE.</i> |

| | |
|--|--|
| LEADER (2016) | <i>In patients with type 2 diabetes and high CV risk, the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke was lower with liraglutide than with placebo.</i> |
| SUSTAIN-6 (2016) | <i>In patients with type 2 diabetes, the rate of CV death, nonfatal MI, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide.</i> |
| EXSCEL (2017) | <i>Among patients with type 2 diabetes with or without previous CV disease, the incidence of MACE did not differ significantly between patients who received exenatide and those who received placebo.</i> |
| PIONEER 6 (2019) | <i>In patients at high CV risk, the CV risk profile of oral semaglutide was not inferior to placebo.</i> |
| Harmony Outcomes (2018) | <i>In patients aged ≥ 40 years with T2DM, prior atherosclerotic CV disease, and suboptimal glycemic control, albiglutide was superior to placebo with respect to MACE.</i> |
| REWIND (2019) | <i>Dulaglutide is superior to placebo in improving glycemic control and reducing CV events in patients with type 2 DM and higher CV risk.</i> |

Adverse effects:

- The most common side effects are GI symptoms, including nausea, vomiting, diarrhoea or constipation.
- Increased risk of gall-bladder diseases like gallstone and cholecystitis.

Inotropes and Vasopressors

Table 36-56: Positive inotropes and/or vasopressors used to treat acute heart failure:

| | Adrenergic receptor antagonists | | | | Ca sensitizer | PDE III inhibitor |
|------------------------------------|---|----------------------------------|----------------------------------|--------------------------------|--|----------------------------|
| | Dopamine | Dobutamine | Norepinephrine | Epinephrine | Levosimendan | Milrinone |
| Mechanism of action | <i>Dopa</i> > β HD, α | β_1 > β_2 > α | α > β_1 > β_2 | $\beta_1 = \beta_2$ > α | Calcium sensitization (HD) > PDE III inhibition | PDE III inhibition |
| Inotropic effect | ↑↑ | ↑↑ | ↑ | ↑↑ | ↑ | ↑ |
| Arterial VD | ↑↑ (renal, LD) | ↑ | 0 | ↑ | ↑↑ | ↑↑↑ |
| Vasoconstriction | ↑↑ (HD) | ↑ (HD) | ↑↑ | ↑ (HD) | 0 | 0 |
| Pulmonary VD | | ↑ or 0 | ↓ or 0 | ↓ or 0 | ↑↑ | ↑↑ |
| Elimination t_{1/2} | 2 min | 2.4 min | 3 min | 2 min | 1.3 h | 2.5 h |
| Infusion dose | <ul style="list-style-type: none"> ○ <3 µg/kg/min: renal VD ○ 3–5 µg/kg/min: inotropic ○ >5 µg/kg/min: vasoconstrictor | 1–20 µg/kg/min | 0.02–10 µg/kg/min | 0.05–0.5 µg/kg/min | 0.05–0.2 µg/kg/min | 0.375–0.75 µg/kg/min |
| Bolus dose | No | No | No | 1 mg during CPR every 3–5 min | 6–12 µg/kg over 10 min (optional) | 25–75 µg/kg over 10–20 min |

| Table 36-57: Inotropic mechanisms and drugs: | |
|--|--|
| Inotropic mechanism | Drugs |
| <i>Sodium-potassium-ATPase inhibition</i> | <i>Digoxin</i> |
| <i>β-Adrenoceptor stimulation</i> | <i>Dobutamine, dopamine</i> |
| <i>Phosphodiesterase inhibition</i> | <i>Enoximone, milrinone</i> |
| <i>Calcium sensitization</i> | <i>Levosimendan</i> |
| <i>Na-K ATPase inhibition + SERCA activation</i> | <i>Istaroxime</i> |
| <i>Acto-myosin cross-bridge activation</i> | <i>Omecamtiv mecarbil</i> |
| <i>SERCA activation</i> | <i>Gene transfer</i> |
| <i>SERCA activation plus vasodilation</i> | <i>Nitroxyl donor; CXL-1020</i> |
| <i>Ryanodine receptor stabilization</i> | <i>Ryanodine receptor stabilizer; S44121</i> |
| <i>Energetic modulation</i> | <i>Etomoxir, pyruvate</i> |

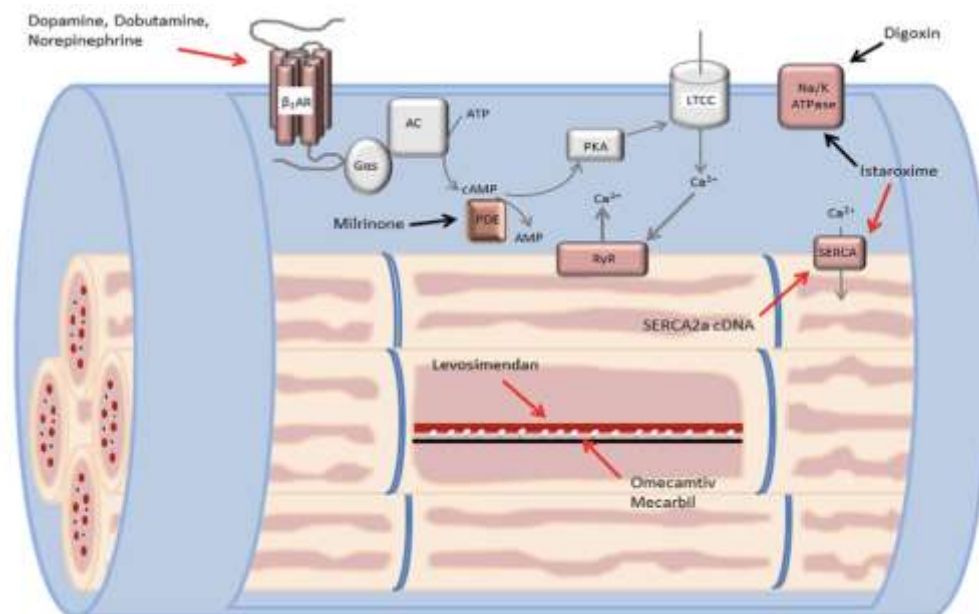


Figure 36-13: Diagram of Intracellular Signaling Cascades Within Cardiomyocytes Altered by Inotropes.

Red arrows denote agonists, whereas **black arrows** signify antagonists. AC= adenylyl cyclase; ADP= adenosine diphosphate; ATP= adenosine triphosphate; B1AR= b1-adrenergic receptor; cAMP= cyclic adenosine monophosphate; LTCC= L-type calcium channel; PDE= phosphodiesterase; PKA= protein kinase A; RyR= ryanodine receptor; SERCA= sarco/endoplasmic reticulum Ca2p-ATPase.

Dopamine, dobutamine, and norepinephrine activate the b1-adrenergic receptor, which activates the G protein Gas, which in turn, activates adenylyl cyclase. Adenylyl cyclase converts ATP to cAMP. cAMP can activate PKA, which then phosphorylates the L-type calcium channel, among other targets. cAMP is converted to AMP by PDE.

Milrinone inhibits PDE-3 thereby increasing the effective concentration of cAMP. Calcium influx through the L-type calcium channel induces activation of ryanodine receptors, leading to calcium-induced calcium release. Free intracellular calcium interacts with troponin C, which changes the binding properties of tropomyosin and allows the interaction between actin and myosin.

Levosimendan potentiates the interaction between troponin and calcium. It may also have PDE-3 inhibitor activity.

Omecamtiv mecarbil increases the rate of ATP turnover and slows the rate of ADP release thereby increasing the number of myosin molecules bound to actin at any given time. SERCA is responsible for uptake of calcium into the sarcoplasmic reticulum while the Na/K ATPase participates in resetting the membrane potential of the cell.

Istaroxime inhibits Na/K ATPase while also potentiating SERCA.

Digoxin inhibits the Na/K ATPase. **Source:** Francis GS, Bartos JA, Adatya S. Inotropes. Journal of the American College of Cardiology. 2014 May 27;63(20):2069-78.

Dobutamine

Mechanism of action:

Dobutamine is a synthetic analog of dopamine, with strong β_1 agonist activity as well as minor effects on β_2 - and α_1 -receptors. β_1 stimulation enhances cardiac contractility through increases in intracellular cyclic adenosine monophosphate (cAMP) and calcium.

Adverse effects:

- Tachyarrhythmia (~10%): at any infusion dose, particularly in cases of myocarditis and electrolyte imbalance.
- Hypertension (7.5%): At low doses, β_2 -stimulation generally offsets α_1 -adrenergic activity, resulting in peripheral artery vasodilation that occasionally may lead to symptomatic hypotension. At higher doses, though, peripheral vasoconstriction predominates through vascular α_1 -receptor stimulation.
- Eosinophilic myocarditis ($\leq 7\%$) after prolonged infusion.

Cautions:

- Dobutamine increases heart rate and myocardial oxygen demand and should be used cautiously in patients with recent myocardial ischemia.
- β receptors may be downgraded or therapeutically blocked in patients with advanced HF so that intolerance to dobutamine may ensue.

Dopamine

Mechanism of action:

Dopamine is a catecholamine-like agent, with complex effects that vary greatly with dose:

- **At low doses**, dopamine acts on dopamine-1 receptors to dilate renal, splanchnic, and cerebral arteries ⁽¹⁾.
- **At intermediate doses**, dopamine acts as a precursor in the synthesis of norepinephrine, an agonist of both adrenergic and dopaminergic receptors, and an inhibitor of NE reuptake, increasing SV and CO with variable effects on HR. Both the β_1 -stimulation and the rapid release of NE can precipitate tachycardia as well as atrial and ventricular arrhythmias.
- **At higher doses**, dopamine stimulates α -receptors leading to pulmonary and peripheral vasoconstriction.

Cautions:

- Use caution in myocardial ischemia, occlusive vascular disease and ventricular arrhythmias.
- Use caution in patients taking MAO inhibitors; prolong hypertension may occur with concurrent use.
- Discontinuation from high infusion rates should be done gradually to no less than 3 $\mu\text{g/kg/min}$, to minimize potential hypotensive response of low dose dopamine.

Epinephrine

Epinephrine is the first-line vasopressor for cardiac arrest and anaphylactic shock.

Mechanism of action:

It acts as a complete β receptor agonist, with dose-dependent α -agonism effect at higher doses. At lower doses, epinephrine acts predominantly on β_1 -receptors, with less prominent effects on β_2 and α_1 , resulting in an overall increase in CO with balanced vasodilator and vasoconstrictor effects. At higher doses, it increases SVR and BP, with combined inotropic and vasopressor effect.

(1) Although it has been proposed that dopamine might improve renal blood flow promoting natriuresis through direct distal tubular effects, data supporting that are limited. The **DAD-HF** study suggested that a combination of low-dose furosemide and low-dose dopamine as a continuous infusion for 8 hours was equally effective as high-dose furosemide but associated with improved potassium homeostasis and preservation of renal function. These findings are consistent with the **ROSE-ADHF** trial, which found that neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function in patients with ADHF. Notably, both DAD-HF II and ROSE-ADHF studies showed a higher incidence of tachycardia in the dopamine group.

Adverse effects:

- Common side effects, particularly at high doses, include tachycardia, arrhythmias, poor peripheral perfusion, headaches, anxiety, cerebral hemorrhage, and pulmonary edema.
- There is also a risk of local tissue necrosis with extravasation: To prevent sloughing and necrosis in areas has extravasation, infiltrate the area with 10-15 mL of 0.9% NaCl solution containing phentolamine 5-10 mg.

Cautions:

- Use caution in patients with cardiac disease, angina (especially with history of CAD) or that are receiving drugs that sensitize the myocardium; treatment may induce cardiac arrhythmias.
- Pulmonary edema may occur as the result of cardiac stimulation and peripheral constriction.
- Decreased urine output may occur as the result of renal blood vessel constriction.
- Injection into buttock may not provide effective treatment of anaphylaxis.

Isoproterenol

Mechanism of action:

Strong beta-1 & beta-2 effects resulting in relaxation of GI, bronchial, and uterine smooth muscle; may increase vasodilation of peripheral vasculature, and heart rate and contractility.

This relatively pure β -stimulant should be considered in cardiogenic shock secondary to bradycardia or when excessive β -blockade is thought to be contributing to hypoperfusion. It increases inotropy and chronotropy through β_1 -stimulation, with a variable response on BP, depending upon the degree of concomitant β_2 vasodilator stimulation.

Adverse effects:

- Palpitations, sinus tachycardia, and more serious arrhythmias.

- Other side effects are hypotension, angina pectoris, flushing, headache, restlessness, and sweating.
- Patients with IHD may be at higher risk of further myocardial ischemia due to increased O₂ consumption.

Cautions:

- May cause thyroid storm in susceptible patients with hyperthyroidism.
- May transiently increase blood glucose levels.
- Isoproterenol hydrochloride injection should be started at lowest recommended dose and gradually increased if necessary while carefully monitoring the patient.

Phosphodiesterase Inhibitors (Milrinone and Enoximone)

Mechanism of action:

PDE-3 inhibitors decrease the rate of cAMP degradation, leading to enhanced inotropy, chronotropy, and lusitropy in cardiomyocytes. They also cause significant peripheral and pulmonary vasodilation via inhibition of vascular PDE, reducing preload and afterload while increasing contractility.

Adverse effects:

Major side effects include: ventricular arrhythmias (>10%), SVT (4%) and hypotension (3%).

Cautions:

- The increased levels of myocardial cAMP predispose to life-threatening arrhythmias, and the routine use of these agents for periods longer than 48 hours is not recommended.
- The dose requires adjustments in the presence of renal dysfunction.

- Discontinue therapy if symptoms of hepatotoxicity (eg., increased LFTs) occur.

N.B: Since PDE-3 inhibitors do not act via β -receptor stimulation, their effects are not offset by concomitant β -blocker therapy as are those of dobutamine or dopamine. Additionally, this independence of adrenergic pathways also allows for synergistic effects with the β -agonist inotropes.

Calcium Sensitizers (Levosimendan)

Mechanism of action:

- Calcium sensitizers increase the sensitivity of troponin C fibers to ionic calcium that is already available in the cytoplasm, improving myocardial contractility with no additional calcium overload and minimal increase in oxygen demand.
- Calcium sensitizers share some PDE-3 inhibitor activity that may be partially responsible for their inotropic and vasodilator properties.
- Levosimendan exerts additional pleiotropic effects through the opening of potassium dependent ATP channels in vascular smooth muscle cells and mitochondria.

Indications:

Levosimendan is indicated as short-term therapy for patients with ADHF who need inotropic support in the absence of severe hypotension. Due to an active long-acting metabolite, the hemodynamic effects of levosimendan can last for up to at least a week after stopping the infusion. Despite a dose-dependent improvement in indices of cardiac performance, including a reduction in PCWP and afterload and an increase in CO, there is limited evidence of clinical benefit from levosimendan therapy.

Cautions:

Levosimendan therapy is associated with more episodes of atrial fibrillation and hypokalemia.

Omecamtiv Mecarbil

Omecamtiv mecarbil is a direct cardiac myosin activator that enhances effective actin-myosin cross-bridge formation and creates a force-producing state that is not associated with cytosolic calcium accumulation. Thus, omecamtiv mecarbil acts as a calcium-sensitizer with pure inotropy action and no pleiotropic effects.

Earlier studies have shown that it is safe, well tolerated, and produces dose-dependent increases in systolic ejection time, SV, EF, and fractional shortening. In the ATOMIC-AHF trial, IV omecamtiv mecarbil did not meet the primary outcome of dyspnea improvement in patients with ADHF compared to placebo, except in the higher-dose group. However, it increased systolic ejection time and decrease LV endsystolic diameter.

Istaroxime

Istaroxime is an investigational drug that mediates lusitropism through inhibition of sodium-potassium ATPase and stimulation of the sarcoendoplasmic reticulum calcium ATPase type 2a (SERCA2a).

In the phase 2 HORIZON-HF trial, the addition of istaroxime to standard therapy lowered PCWP and HR and increased systolic BP in patients with ADHF. Also, higher doses of istaroxime appeared to be associated with more improvement in diastolic function. The role of this agent remains uncertain at this time.

Norepinephrine

Mechanism of action:

NE has a high affinity for α 1-receptors and moderate affinity for β -adrenergic receptors, resulting in marked vasoconstriction with mild to modest increase in HR, CO, and myocardial oxygen demand.

Indications:

NE is the vasopressor of choice for generalized shock. The SOAP II trial evaluated first-line vasopressor selection in patients with generalized shock and showed that, among the prespecified cardiogenic shock subgroup, dopamine was associated with a higher risk of death and arrhythmia when compared to NE.

Sepsis & Septic Shock: 0.01 - 3.3 mcg/kg/min IV infusion (Hollenberg 2009)

Adverse effects:

- Reflex bradycardia
- Hypertension
- Arrhythmias
- Dyspnea, with or without respiratory difficulty
- Headache
- Risk of local tissue necrosis with extravasation

Cautions:

- To prevent sloughing and necrosis in areas in which extravasation has taken place, area should be infiltrated as soon as possible with 10 - 15 mL of saline solution containing from 5 mg to 10 mg of phentolamine, an adrenergic blocking agent.
- Do not administer NaHCO₃ through an IV line containing norepinephrine.

Drug interactions:

- Concomitant use with some general anesthetics cyclopropane, halothane: Both increase cardiac autonomic irritability and seem to sensitize the myocardium to action of epinephrine or norepinephrine.
- Linezolid increases effects of norepinephrine by pharmacodynamic synergism. Contraindicated. Risk of acute hypertensive episode.

Other Vasopressors: The most often used vasopressors are Norepinephrine, high-dose dopamine, high-dose epinephrine, vasopressin, and phenylephrine.

Vasopressin is an endogenous vasopressor stored mainly in the posterior lobe of the pituitary gland and myocardium. Currently, vasopressin is used as a second-line agent in refractory vasodilatory shock, particularly septic shock or anaphylaxis that is unresponsive to epinephrine.

Phenylephrine is a selective α_1 -receptor agonist with potent arterial vasoconstrictor effect and minimal cardiac inotropy or chronotropy. It is particularly useful in patients with severe hypotension related to systemic vasodilation, such as septic shock, rather than to a decrease in CO. Thus, it should be reserved for patients in whom NE is contraindicated due to arrhythmias or who have failed other vasopressors.

Digoxin

Mechanism of action:

- Digoxin inhibits Na-K ATPase, which in turn causes increased availability of intracellular calcium in the myocardium and conduction system. Inotropy and automaticity are subsequently increased while conduction velocity is reduced.
- Therapy indirectly causes parasympathetic stimulation of autonomic nervous system, with consequent effects on the SA and AV nodes.
- Digoxin reduces catecholamine reuptake at nerve terminals, rendering blood vessels more sensitive to endogenous or exogenous catecholamines.

At higher concentration, increases sympathetic outflow from the CNS to both cardiac and peripheral sympathetic nerves. It also allows progressive efflux of intracellular potassium, with consequent increase in serum potassium levels.

Indications & clinical evidence:

Table 36-58: Clinical trials of Digoxin:

| Trial (date) | Summary |
|--|--|
| Heart Failure with reduced ejection fraction: | |
| DIG (1997) | <i>In patients with LVEF \leq 45%, addition of digoxin reduces hospitalization rate, but does not impact mortality, among patients with HFrEF.</i> |
| Heart Failure with preserved ejection fraction: | |
| Ancillary DIG (2006) | <i>In ambulatory chronic heart failure patients with normal sinus rhythm and EF > 45%, digoxin had no effect on all-cause or cause-specific mortality or on all-cause or CV hospitalization.</i> |
| Atrial Fibrillation: | |
| RATE-AF (2020) | <i>In patients with permanent AF, lenient rate control strategy (resting HR < 110 bpm) is as effective as strict rate control (resting HR < 80 bpm and HR during moderate exercise < 110 bpm) and is easier to achieve.</i> |

Adverse effects:

- Dizziness (4.9%)
- Diarrhea (3.2%)
- Headache (3.2%)
- Visual disturbance (blurred or yellow vision)
- Risk of advanced or complete heart block in patients with sinus node disease and AV block
- ECG features:
 - down-sloping ST depression ('reverse tick', 'scooped out')
 - flattened/inverted T wave.
 - short QT interval

Contraindications:

- Hypersensitivity
- Ventricular fibrillation

Cautions:

- Not recommended in patients with acute myocardial infarction and myocarditis
- Very narrow margin between effective therapeutic and toxic dosages: Therapeutic range, 0.5-2 ng/mL (target 0.5-1 ng/mL); toxic range, > 2.5 ng/mL
- Less effective in presence of hypokalemia or hypocalcemia; avoid hypercalcemia or hypomagnesemia, which may predispose to serious arrhythmias.
- Do not switch between different PO forms or between brand and generic forms; bioavailability varies.
- Serum levels drawn within 6-8 hrs of dose will be falsely high because of prolonged distribution phase.
- Increased risk of estrogen-like effects in geriatric patients.

- Beriberi heart disease may not respond adequately if underlying thiamine deficiency not corrected.

Sodium Nitroprusside

Mechanism of action:

Relaxes vascular smooth muscle to reduce afterload and preload by producing NO. The use of SNP in patients with ADHF results in a significant decrease in systemic BP, right atrial pressure (RAP), pulmonary arterial pressure (PAP), PCWP, SVR, and pulmonary vascular resistance (PVR).

Indications:

- *Hypertensive Crisis*: initial infusion rate: 0.3 mcg/kg/min; evaluate BP for at least 5 minutes before titrating to a higher or lower dose to achieve desired BP. Not to exceed 10 mcg/kg/min.
- Sodium Nitroprusside is particularly effective in the setting of ADHF secondary to elevated afterload such as acute aortic or mitral regurgitation, ventricular septal rupture, or hypertensive emergency.

Adverse effects:

- *Hypotension* may occur, leading to irreversible ischemic injury or death. Nitroprusside-induced hypotension will be self-limited within 1-10 minutes after discontinuation of therapy (short half-life); during these few minutes, it may be helpful to put the patient into a head-down (Trendelenburg) position to maximize venous return; if hypotension persists more than a few minutes after discontinuation of infusion therapy is not the cause, and the true cause must be sought.
- *Cyanide toxicity* (which may be fatal): secondary to nitroprusside metabolism to cyanide especially when large doses used for long periods of time. It is more common in patients with renal and/or hepatic dysfunction. The first sign of cyanide toxicity is lactic acidosis. Cyanide toxicity may present as venous hyperoxemia with bright red venous blood, as cells become unable to extract oxygen delivered to them. The most common side effects of thiocyanate toxicity are mental status changes, nausea,

and abdominal pain. Thiocyanate can be removed with dialysis, and cyanide toxicity has been successfully managed with infusions of thiosulfate, sodium nitrate, and hydroxycobalamin.

- *Rebound hypertension* due to sudden withdrawal, so gradual tapering is advised.

Contraindications:

- Hypersensitivity.
- SNP is not recommended in the setting of ACS: significant vasodilation of the intramyocardial vasculature may cause a “coronary steal” phenomenon.
- Compensatory HTN (eg, AV shunt or aortic coarctation).
- Certain rare conditions, eg, congenital optic atrophy, tobacco amblyopia.
- Treatment of acute CHF associated with reduced peripheral vascular resistance such as high-output heart failure that may be seen in endotoxic sepsis.
- Therapy can cause increases in intracranial pressure; in patients whose ICP is already elevated.

Nesiritide

Mechanism of action:

Nesiritide is a synthetic analogue form of the human B-type natriuretic peptide (BNP), manufactured from E. coli with recombinant DNA technology. It increases cGMP in vascular smooth muscle resulting in vasodilation, reduce pulmonary capillary wedge pressure (PCWP) and mild increases in CO.

Indications and Clinical evidence:

Table 36-59: Clinical trials of Nesiritide:

| Trial (date) | Summary |
|---|---|
| Acute Decompensated Heart failure: | |
| Because of its high cost and lack of clear clinical benefit beyond other vasodilator therapies, such as NTG or SNP, nesiritide is not recommended as a first-line drug for patients with ADHF. However, in selected patients who remain symptomatic despite standard therapy, a trial of nesiritide may be helpful. | |
| VMAC (2002) | <i>In inpatients with dyspnea at rest from decompensated CHF, nesiritide improves hemodynamic function and some self-reported symptoms more effectively than i.v nitroglycerin or placebo.</i> |
| ASCEND-HF (2011) | <i>In patients with acute heart failure, nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization and had a small, nonsignificant effect on dyspnea when used in combination with other therapies. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in patients with acute heart failure.</i> |
| ROSE-ADHF (2013) | <i>In hospitalized patients with acute heart failure and renal dysfunction (eGFR of 15-60 mL/min/1.73 m²), neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.</i> |

Adverse effects:

- Hypotension (4-35%)
- Serum creatinine raised (17-28%)
- Ventricular tachycardia (3-10%)
- Headache (7-9%)

Contraindications:

- Atrial/ventricular arrhythmias, constrictive pericarditis, restrictive or obstructive cardiomyopathy, pericardial tamponade, significant valvular stenosis, suspected low cardiac filling pressures.
- Persistent systolic BP < 100 mmHg.

Nicorandil

Mechanism of action:

Nicorandil stimulates ATP-sensitive potassium channels (KATP) in vascular smooth muscle. Opening of the potassium channel leads to arterial vasodilatation and reduced afterload, while the nitrate effect leads to reduced preload.

Indications and Clinical evidence:

Table 36-60: Clinical trials of Ranolazine:

| Trial (date) | Summary |
|---|---|
| Chronic Coronary Syndrome: | |
| Nicorandil is a nitrate derivative of nicotinamide that can be used for the prevention and long-term treatment of angina, and may be added after b-blockers and CCBs. It is EMA but not FDA approved. Long-term use of oral nicorandil may stabilize coronary plaque in patients with stable angina. Nicorandil may also be particularly useful in patients with hypotension or bradycardia, as it has minimal effects on these haemodynamic parameters. | |
| IONA (2002) | <i>Nicorandil showed a significant improvement in outcome of patients with stable angina due to a reduction in major coronary events.</i> |

Adverse effects:

- *Headache*: occurs commonly, especially in the early phase of treatment; consider a lower starting dose
- *Dizziness and hypotension*: especially at higher doses
- *Peripheral vasodilation leading to flushing*: occurs commonly.

- *Ulceration*: GI ulceration, skin ulceration, and ulcers of the mucosal membranes have been reported. These tend to be refractory to treatment and most only respond to withdrawal of nicorandil treatment.
- *Hypotension*
- *Angioedema*: occurs uncommonly.

Contraindications:

- Left ventricular failure with low filling pressures and hypotension.
- Hypersensitivity to nicorandil.
- Pregnancy and breast-feeding

Drug interactions:

- *Antihypertensives*: enhanced hypotensive effect with the addition of nicorandil
- *Oral corticosteroids*: increase of gastric erosions when used in combination with nicorandil.
- Concomitant use of nicorandil and PDE-5 inhibitors is contraindicated due to the risk of severe hypotension.

Ranolazine

Mechanism of action:

The mode of action of ranolazine is not well understood, despite the agent being in use for a number of years. Speculation on its mode of action focuses on ***selective inhibition of the late inward sodium current in cardiac cells***. Reduced accumulation of sodium leads to a lower intracellular calcium load, facilitating myocardial relaxation and reducing diastolic stiffness.

Ranolazine reduces the abnormalities of ventricular repolarization and contractility seen during episodes of ischaemia, with a resultant improvement in myocardial function and perfusion.

The antianginal effects of ranolazine are independent of changes in blood pressure and heart rate.

Indications and Clinical evidence:

| Table 36-61: Clinical trials of Ranolazine: | |
|--|--|
| Trial (date) | Summary |
| Chronic Coronary Syndrome: | |
| The EMA approved ranolazine in 2009 for add-on treatment in stable angina in patients inadequately controlled by or intolerant to first-line agents (beta-blockers and/ or calcium antagonists) to reduce angina frequency and improve exercise tolerance. Ranolazine may also be particularly useful in patients with hypotension or bradycardia, as it has minimal effects on these haemodynamic parameters. | |
| MARISA (2004) | <i>In patients with angina-limited exercise, ranolazine monotherapy was well tolerated and increased exercise performance throughout its dosing interval at all doses studied without clinically meaningful hemodynamic effects.</i> |
| CARISA (2004) | <i>In adults with symptomatic chronic angina, twice-daily doses of ranolazine increased exercise capacity and provided additional antianginal relief to symptomatic patients with severe chronic angina taking standard doses</i> |

| | |
|------------------------------|--|
| | <i>of atenolol, amlodipine, or diltiazem, without evident adverse, long-term survival consequences over 1 to 2 years of therapy.</i> |
| ERICA (2006) | <i>In patients with coronary disease and ≥ 3 anginal attacks/week despite maximum recommended dosage of amlodipine (10 mg/day), ranolazine significantly reduced frequency of angina and nitroglycerin consumption compared with placebo and was well tolerated.</i> |
| MERLIN-TIMI-36 (2007) | <i>In patients within 48 hours of ischemic symptoms, the addition of ranolazine to standard treatment for ACS was not effective in reducing MACE. Ranolazine did not adversely affect the risk of all-cause death or symptomatic documented arrhythmia.</i> |

Adverse effects:

- *Gastrointestinal*: diarrhea, constipation, nausea, and vomiting occur commonly. Anorexia, reduced appetite, and dehydration occur uncommonly.
- *Syncope, postural dizziness, headache*: may require dose reduction.
- *Skin*: allergic dermatitis, urticaria, rash, pruritis, hyperhidrosis
- *CNS*: somnolence, tremor, fatigue. Rarely, disorientation, amnesia, depressed level or loss of consciousness
- *Eye and ear*: blurred vision, visual disturbance, vertigo, tinnitus.
- *QT prolongation*.

Contraindications:

- Severe renal impairment (CrCl < 30 mL/min).
- Moderate to severe hepatic impairment.
- Pregnancy and Breast-feeding.

Cautions:

Ranolazine clearance is reduced by renal and hepatic impairment, so initiate and undertake dose titration carefully in patients with mild to moderate renal impairment (CrCl 30–80 mL/min), mild hepatic dysfunction, or moderate to severe HF (NYHA III–IV), elderly patients, and patients with low body weight (> 60 kg).

Monitoring:

- Blood pressure and pulse should be checked at baseline and within 4 weeks of initiation or dose change. Ranolazine usually has minimal effects on blood pressure and heart rate.
- ECG monitoring may be considered after initiation to ensure no significant QTc prolongation.
- Small increases in S. creatinine have been noted during treatment, but this is not linked to renal toxicity.

Drug interactions:

- *Anti-arrhythmics*: avoid concomitant use with disopyramide.
- *Antibacterials*: clarithromycin and telithromycin possibly increase ranolazine levels; avoid concomitant use.
- *Rifampicin* reduces ranolazine levels; avoid concomitant use.
- *Antifungals*: ketoconazole, itraconazole, posaconazole, voriconazole increase plasma levels of ranolazine; avoid concomitant use
- *Antivirals*: possible increase in ranolazine levels; check individual agents for details
- *Beta-blockers*: avoid concomitant use with sotalol
- *Grapefruit juice*: may increase ranolazine levels; avoid concomitant consumption.

Trimetazidine

Mechanism of action:

Trimetazidine inhibits beta-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation.

Indications:

Trimetazidine (35 mg twice daily) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the EMA. In diabetic persons, trimetazidine improved HbA1c and glycaemia, while increasing forearm glucose uptake.

Adverse effects:

- Gastric discomfort
- Nausea
- Headache
- Movement disorders

Contraindications:

- Allergy
- Parkinson's disease and motion disorders [such as tremor (shaking), muscle rigidity and walking disorders and restless leg syndrome].
- Severe renal impairment

Cautions:

- Moderate renal impairment

- Elderly

Drugs used in Pulmonary Hypertension

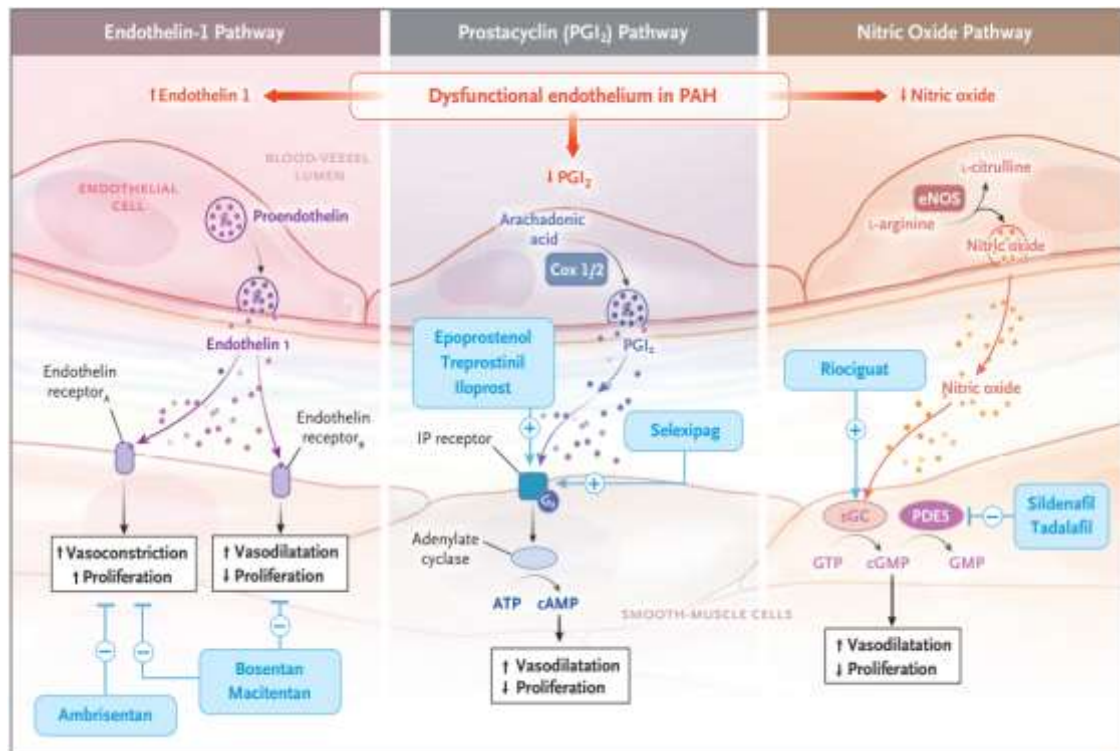


Figure 36-14: Three Classic Pathways of Targeted Therapy for PAH. Current targeted therapy is aimed at correcting endothelial dysfunction by inhibiting the endothelin pathway and enhancing the prostacyclin (PGI₂) and NO pathways. Endothelin 1 (ET1), which is increased in PAH, can bind to either the endothelin A (ETA) receptor, causing vasoconstriction (of smooth muscle cells) and cell proliferation, or the endothelin B (ETB) receptor, causing vasodilatation and antiproliferation. The expression and function of the PGI₂ and NO pathways are decreased in PAH, resulting, respectively, in diminished cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are second messengers responsible for vasodilatation and antiproliferation. Agents that increase cAMP include PGI₂ analogues given intravenously (e.g., epoprostenol and treprostinil), subcutaneously (e.g., treprostinil), by inhalation (e.g., iloprost and treprostinil), or orally (treprostinil), or with the use of oral PGI₂ receptor (IP) agonists (e.g., selexipag). Increased cGMP release can be achieved with inhaled NO (used essentially in the catheterization laboratory or intensive care unit), which stimulates soluble guanylate cyclase (sGC), or by inhibiting phosphodiesterase type 5 (PDE5, which degrades cGMP into GMP) with the use of oral PDE5 inhibitors (sildenafil or tadalafil). Direct sGC stimulators (e.g., oral riociguat) can increase the release of cGMP independently of NO release. **Source:** Hassoun PM. Pulmonary Arterial Hypertension. *N Engl J Med.* 2021 Dec 16;385(25):2361-2376. doi: 10.1056/NEJMra2000348. PMID: 34910865.

Endothelin-Receptor Antagonists

(Bosentan, Ambrisentan, and Macitentan)

Three main kinds of Endothelin-Receptor Antagonists exist:

- Selective ETA receptor antagonists (Sitaxentan, Ambrisentan), which affect endothelin A receptors.
- Dual antagonists (Bosentan and Macitentan), which affect both endothelin A and B receptors.
- Selective ETB receptor antagonists (BQ-788 and A192621) are used in research only.

Mechanism of action:

The endothelin (ET) system is comprised of 4 active ETs, with ET-1 being the predominant isoform in the cardiovascular system. Two receptor subtypes, ETA and ETB, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. Primary actions of ETA are vasoconstriction and cell proliferation, while the predominant actions of ETB are vasodilation, antiproliferation, and ET-1 clearance. High affinity endothelin (ETA) receptor subtype antagonist, resulting in inhibition of vasoconstriction.

Indications and Clinical evidence:

| Table 36-62: Clinical trials of Endothelin-Receptor Antagonists: | |
|--|--|
| <i>Trial (date)</i> | <i>Summary</i> |
| Pulmonary Arterial hypertension: | |
| BREATHE-1 (2002) | <i>The endothelin-receptor antagonist bosentan is beneficial in patients with pulmonary arterial hypertension and is well tolerated at a dose of 125 mg twice daily.</i> |
| BREATHE-2 (2004) | <i>30 patients were randomized in a 2 to 1 fashion to receive epoprostenol with bosentan or epoprostenol alone over a 16-week period. The trial failed to show any significant difference between the groups with respect to hemodynamics or 6-minute walk distance.</i> |

Adverse effects:

- Peripheral edema (17%).
- Headache (15%).
- Nasal congestion (6%).
- Palpitations (5%).
- Constipation (4%).
- Dyspnea (4%).
- Flushing (4%).

Contraindications:

- *Pregnancy: exclude pregnancy before starting treatment, monthly during treatment, and 1 month after stopping treatment.*
- *Idiopathic pulmonary fibrosis.*
- *Moderate to severe hepatic impairment: prolonged use may be associated with hepatic cirrhosis.*

Cautions:

- *Discontinue in patients with elevated aminotransferases > 5 x ULN, or if elevations are accompanied by bilirubin > 2 X ULN, or signs/symptoms of liver dysfunction.*
- *Risk of fluid retention and peripheral edema; more common in combination with tadalafil, than with ambrisentan or tadalafil alone.*
- *Development of acute pulmonary edema during therapy initiation may occur; if happens, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed therapy should be discontinued.*

Drug interactions:

- *Ketoconazole approximately doubles the exposure to bosentan because of inhibition of CYP3A4.*

- *Coadministration of ciclosporin and bosentan markedly increases initial bosentan trough concentrations.*

Prostacyclin Analogues

(Epoprostenol, Iloprost and Treprostinil)

Mechanism of action:

Prostacyclin (PGI₂) and its analogues bind the prostacyclin receptor (IP receptor) on the cell surface membrane. Once engaged, the IP receptor couples the G-protein G_s and activates adenylyl cyclase, producing cAMP and leading to relaxation in smooth muscle cells and antithrombosis in platelets. Like PGI₂, treprostinil engages the IP receptor, but also demonstrates strong affinity to the EP₂ and DP₁ cell surface receptors.

Epoprostenol is distinguished from epoprostenol by its much longer half-life (4 hours versus 2.7 minutes for epoprostenol) and greater flexibility with respect to route of administration.

Indications:

Indicated for treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise.

Adverse effects:

- Flushing
- Jaw pain
- Rash.
- Hypotension.
- Headache.
- Myalgia.
- Diarrhea.

- Nausea and Vomiting.
- Flu-like symptoms.
- Anxiety.
- Infusion site reaction, pain (in treprostinil)

Contraindications:

- Hypersensitivity.
- Chronic use in patients with CHF due to left ventricular systolic dysfunction.
- Development of pulmonary edema during initial dose titration.

Cautions:

- During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output reported rarely; in such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated.
- Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage may result in symptoms associated with rebound pulmonary hypertension.
- Use caution in patients with risk factors of bleeding.
- Blood stream infections may develop from chronic infusions using an indwelling central venous catheter.
- Administer anticoagulant therapy to patients receiving therapy to reduce risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale.

Prostacyclin receptor (IP receptor) agonist
(Selexipag)

Mechanism of action:

Selexipag (Uptravi®) is a first-in-class, long-acting, selective prostacyclin receptor (IP receptor) agonist. Oral selexipag is rapidly hydrolyzed into the active metabolite. Both selexipag and its active metabolite have high selectivity for the IP receptor and act by potentially increasing intracellular cyclic adenosine monophosphate (cAMP) levels, which inhibits pulmonary arterial smooth muscle cell contraction and smooth muscle cell proliferation.

The recommended initial dosage is 200 µg given twice daily. Subsequently, the dosage is increased by increments of 200 µg twice daily, usually every week (maximum dosage of 1600 µg twice daily).

Indications and Clinical evidence:

Selexipag has recently been approved in several countries including in the EU for the long-term treatment of PAH in adult patients with WHO FC II or III as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor or as monotherapy in patients who are not candidates for these therapies, and in the USA for the treatment of PAH to delay disease progression and reduce the risk of hospitalization for PAH.

| Table 36-63: Clinical trials of Prostacyclin receptor agonist: | |
|--|---|
| Trial (date) | Summary |
| Pulmonary Arterial hypertension: | |
| GRIPHON (2015) | <i>Oral selexipag (200–1600 µg twice daily, as tolerated) was effective in reducing the risk of mortality and morbidity associated with PAH, as indicated by a significant 40% reduction relative to placebo in the risk of the primary composite endpoint of all-cause death or a complication related to PAH.</i> |

Adverse effects:

The most common adverse events consistent with those known to be associated with epoprostenol and its analogs (i.e., headache, diarrhea, nausea). Generally, these adverse events occurred more frequently during the dose-titration phase than the maintenance phase.

Cautions:

Selexipag should be avoided in patients with severe hepatic impairment (Child-Pugh class C).

Phosphodiesterase-5 Enzyme Inhibitors (Sildenafil and tadalafil)

Mechanism of action:

The two currently approved PDE-5is for the treatment of PAH, sildenafil and tadalafil, both functions to selectively inhibit PDE-5, thus augmenting the availability of cGMP and leading to vasorelaxation. Vardenafil has been studied for use in a PAH population but is not approved for use in PAH by the FDA.

Indications:

The presence of abundant PDE-5 receptors in the pulmonary vasculature makes PDE5 inhibitors an important modality to manage pulmonary hypertension.

Adverse effects:

- Headache (7-16%)
- Flushing (4-10%)

- Epistaxis (8%)
- Dyspepsia (4-8%)
- Altered color vision presenting as a slight and transient blue tinge to the vision - the presence of a high concentration of PDE6 enzyme in rods and cones of retina makes these cells a susceptible target for PDE5 inhibitors, especially with sildenafil which has a high affinity for inhibiting PDE6 in addition to PDE5. This effect has not been shown to be accompanied by any structural and functional changes of the retina.

Cautions:

- Elicits vasodilatory properties, resulting in mild and transient decreases in blood pressure.
- Sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness.
- May cause dose-related impairment of color discrimination; use caution in patients with retinitis pigmentosa.
- Patients should stop sildenafil and seek medical care if a sudden loss of vision occurs in 1 or both eyes, which could be a sign of nonarteritic anterior ischemic optic neuropathy (NAION).

Drug interactions:

- Coadministration with nitrates (either regularly and/or intermittently) and nitric oxide donors due to the risk of fatal hypotension. American College of Cardiology recommends patients taking PDE5Is wait for at least 1 to 2 days after the last PDE5I dose before administering nitrates.
- Coadministration of PDE-5 inhibitors with soluble guanylate cyclase (sGC) stimulators (eg, riociguat); cause hypotension.

Soluble Guanylyl Cyclase (sGC) stimulator
(Riociguat)

Mechanism of action:

Stimulates soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). NO binds to sGC and catalyzes synthesis of cGMP, which in turn activates protein kinase G regulation of cytosolic calcium ion concentration; this cascade changes actin-myosin contractility resulting in vasodilation.

PAH is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway.

Elicits a dual mode of action; riociguat sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding, and also directly stimulates sGC via a different binding site, independently of NO.

Indications and dose:

- Indicated for PAH, (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.
- Indicated for persistent/recurrent CTEPH, (WHO Group 4) after surgical treatment or inoperable CTEPH, to improve exercise capacity and WHO functional class.

Initial dose: 1 mg PO TID; consider 0.5 mg PO TID if patient may not tolerate hypotensive effect.

If systolic blood pressure > 95 mmHg and no symptoms of hypotension, up-titrate dose by 0.5 mg PO TID with dose increases no sooner than 2 weeks apart to highest tolerated dose (not to exceed 2.5 mg PO TID)

If symptoms of hypotension occur, decrease dose by 0.5 mg TID.

Adverse effects:

- Headache (27%)
- Dyspepsia and gastritis (21%)
- Dizziness (20%)
- Nausea (14%)
- Diarrhea (12%)

- Hypotension (10%)
- Vomiting (10%)
- Anemia (7%)

Contraindications:

- Pregnancy: in females of reproductive potential, exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment.
- Patients with pulmonary hypertension associated with idiopathic interstitial pneumonia.

Cautions:

- Reduces blood pressure; consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, or autonomic dysfunction; dose reduction may be required.
- Serious bleeding reported including hemoptysis, vaginal bleeding, catheter site hemorrhage, subdural hematoma, hematemesis, and intra-abdominal hemorrhage.
- Pulmonary vasodilators may significantly worsen cardiovascular status of patients with pulmonary veno-occlusive disease; avoid use in these patients and discontinue if signs of pulmonary edema occur and are confirmed.

Drug interactions:

- Coadministration with nitrates or nitric oxide donors (eg, amyl nitrite), PDE inhibitors (eg, avanafil, sildenafil, tadalafil, vardenafil), or nonspecific PDE inhibitors (eg, dipyridamole, theophylline) because of additive hypotension.

Cardiac Myosin inhibitors

(Mavacamten, Aficamten)

Mechanism of action:

As a cardiac myosin inhibitor, mavacamten directly targets the hypercontractility that plays a central role in the pathophysiology of HCM.

Normally, ATP is hydrolyzed to ADP once bound to myosin through ATPase. When phosphate dissociates from myosin, myosin binds to actin. These bridges are released and shortening occurs as filaments slide past each other, creating myocardial contraction. In HCM, there is an upregulation of cardiac contractility with only 15–20% of myosin heads in an inactive state compared 40–50% in the inactive state normally.

Mavacamten selectively inhibits beta-cardiac myosin ATPase through allosteric binding, decreasing the amount of myosin-actin bridges.

Indications and clinical evidence:

Table 36-64: Clinical trials of Mavacamten:

| Trial (date) | Summary |
|---|--|
| ESC guidelines recommend their use as a second-line treatment when optimal medical therapy with beta blockers, CCBs and/or disopyramide is ineffective or poorly tolerated. | |
| Mavacamten | |
| PIONEER-HCM (2019) | <i>Mavacamten can reduce LVOT obstruction and improve exercise capacity and symptoms in patients with HOCM.</i> |
| EXPLORER-HCM (2020) | <i>Mavacamten significantly improved measures of LV diastolic function and SAM. Improvement in LVOT obstruction, LAVI, and E/e’ was associated with reduction in NT-pro-BNP.</i> |
| VALOR-HCM (2023) | <i>Patients with symptomatic obstructive HCM, there is sufficient and sustained improvement with mavacamten, thereby reducing the need for septal reduction therapy and representing a useful therapeutic option for patients.</i> |

| | |
|---------------------------|--|
| | |
| Aficamten: | |
| REDWOOD-HCM (2023) | <i>Aficamten resulted in substantial reductions in LVOT gradients with most patients experiencing improvement in biomarkers and symptoms. These results highlight the potential of sarcomere-targeted therapy for treatment of HOCM.</i> |

Adverse effects:

- worsening heart failure.
- dizziness (27 %).
- syncope (6 %).
- Acute stress cardiomyopathy
- Atrial fibrillation
- Ventricular tachycardia.

Contraindications:

- Patients with LVEF less than 55 %, given the risk of worsening systolic function.
- Patients taking disopyramide, ranolazine, and concomitant use of non-dihydropyridine CCBs with a beta-blocker.
- Pregnancy as animal studies have shown fetal toxicity. Contraception should continue for at least four months following discontinuation of mavacamten.

Drug interactions:

As Mavacamten is metabolized by CYP2C19 and CYP3A4 enzymes, the concomitant use of moderate-to-strong CYP2C19/CYP3A4 inhibitors (e.g., verapamil and ketoconazole), or inducers (e.g., rifampin), is associated with higher risk for systolic dysfunction, HF exacerbation or loss of medication effectiveness.

Cautions:

- Because mavacamten may cause decreases in LVEF, regular monitoring for clinical symptoms of heart failure and for systolic dysfunction is recommended, including echocardiographic assessments at 4, 8, and 12 weeks after initiating mavacamten treatment and every 12 weeks thereafter.
- For patients with LVEF <50% at any time during mavacamten treatment, temporary or permanent treatment discontinuation is warranted.

Miscellaneous

Colchicine

Mechanism of action:

- Colchicine binds tubulin and inhibits tubulin polymerization, with subsequent disruption of the cellular cytoskeleton, mitosis, and intracellular transport activities.
- Colchicine preferentially accumulates in neutrophils because of the lack of the P- glycoprotein membrane efflux pump and thereby largely affects neutrophil activity:
 - inhibits the directed migration of neutrophils to an inflamed focus (chemotaxis) and decrease adhesion of neutrophils to inflamed endothelium by diminished quantitative surface expression of L- selectin adhesion molecules.
 - inhibits the adhesion of leukocytes to inflamed endothelium by decreased qualitative expression of E-selectin adhesion molecules on endothelial cells, downregulation of tumor necrosis factor receptors on macrophages and endothelial cells, and reduced monocyte/macrophage secretion of tumor necrosis factor α .
 - suppress protein tyrosine phosphorylation in neutrophils with subsequent inhibition of both intracellular mobilization and extracellular release of granular enzymes, such as matrix metalloproteinases, neutrophil elastase, and α -defensins.

Indications and clinical evidence:

Table 36-65: Clinical trials of Colchicine:

| Trial (date) | Summary |
|---------------------------------|---------|
| Non cardiac indications: | |

Colchicine has FDA approval for gout prophylaxis and treatment of acute gouty flares. It also has approval for the treatment of familial Mediterranean fever. Colchicine has been used off-label to treat several other conditions, including hepatic cirrhosis, primary biliary cirrhosis, and pseudogout.

Acute pericarditis:

| | |
|------------------------|--|
| COPE (2005) | <i>Colchicine plus conventional therapy led to a statistically significant benefit over conventional treatment, decreasing the recurrence rate in patients with a first episode of acute pericarditis.</i> |
| ICAP (2013) | <i>In patients with acute pericarditis, colchicine, when added to conventional antiinflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis.</i> |

Recurrent pericarditis:

| | |
|------------------------|--|
| CORE (2005) | <i>Colchicine therapy led to a statistically significant benefit over conventional treatment, decreasing the recurrence rate in patients with a first episode of recurrent pericarditis.</i> |
| CORP (2011) | <i>Colchicine is safe and effective for secondary prevention of recurrent pericarditis.</i> |

Postpericardiotomy syndrome:

| | |
|---------------------------|--|
| COPPS (2010) | <i>Colchicine is safe and efficacious in the prevention of the PPS and its related complications and may halve the risk of developing the syndrome following cardiac surgery.</i> |
| COPPS-2 (2014) | <i>Among patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion. The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.</i> |

Stable coronary artery disease:

| | |
|--------------------------|---|
| LoDoCo (2013) | <i>Colchicine 0.5 mg/day administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease.</i> |
|--------------------------|---|

| | |
|--------------------------------|---|
| LoDoCo2 (2020) | <i>In patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.</i> |
| Acute coronary syndrome | |
| COLCOT (2019) | <i>Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo.</i> |

Dose:

Maintenance dosage is 0.5 to 0.6 mg once or twice daily for acute disease and 0.3 to 0.6 mg daily for chronic prevention. Dosage adjustments are recommended for acutely ill patients with impaired renal function or body weight < 70 kg. Dosage formulations vary on the basis of geographic location, because low-dose formulation tablets are available in 0.6-mg tablets in the United States versus 0.5-mg tablets in other countries. This disparity is evident in the differing dosages used in randomized clinical trials.

Table 36-66: Dosing and Duration for Colchicine Stratified by Indication:

| Clinical Indication | Dose | Duration |
|----------------------------------|-----------------------------|-------------------------------|
| Pericardial disease: | | |
| Acute and recurrent pericarditis | ≥ 70 kg: 0.5 mg twice daily | 3 months |
| Dressler’s syndrome | < 70 kg: 0.5 mg once daily | |
| Postpericardiotomy syndrome | | 1 month after cardiac surgery |
| Atrial fibrillation | | |
| Postoperative AF | 0.5 mg once or twice daily | 1-3 months |
| Postablation AF | | |
| Coronary artery disease | | |
| Stable coronary artery disease | 0.5 mg daily | Possibly indefinite |
| Acute coronary syndrome | | |

Adverse effects:

- GI intolerance including diarrhea, nausea, vomiting, and abdominal pain is the most common adverse effect (10-20% of patients). Lower daily doses at 0.5 mg daily or longer-term treatment durations > 12 weeks may attenuate significant gastrointestinal intolerance.
- At high dosage during prolonged periods of time, colchicine may lead to myelosuppression, neuromuscular toxicity, liver damage, and dermatologic issues.

Tafamidis

Mechanism of action:

Tafamidis is disease-modifying transthyretin (TTR) kinetic stabilizer for treating transthyretin amyloidosis (ATTR amyloidosis). Transthyretin (TTR) is a soluble, tetrameric protein synthesized and secreted by the liver. Conformational change can occur in TTR either spontaneously with age (ATTRwt) or genetic abnormality (ATTRv), leading to destabilization and dissociation into monomers. Tafamidis, a selective stabilizer of TTR, selectively binds to the thyroxine-binding sites and kinetically stabilizes the TTR tetramer. By slowing the dissociation into monomers, the rate-limiting step of amyloid formation, tafamidis slows the disease progression in both cardiomyopathy and peripheral neuropathy.

Indications and clinical evidence:

| Table 36-67: Clinical trials of Tafamidis: | |
|---|---------|
| Trial (date) | Summary |
| <i>Tafamidis is an oral medication for treating cardiomyopathy and peripheral neuropathy due to transthyretin amyloidosis (ATTR).</i> | |

**ATTR-ACT
(2018)**

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo.

Dose:

- In ATTR cardiomyopathy: The recommended dose is either tafamidis meglumine 80 mg (four capsules of 20 mg) or tafamidis 61 mg (single capsule) orally once daily.
- In ATTR peripheral neuropathy: 20 mg of tafamidis meglumine orally once daily.

Adverse effects:

The frequency of adverse events was similar in the tafamidis 80 mg, and the placebo groups. However, data from long-term follow-up and clinical practice settings in ATTR-PN show the following adverse events:

- Headache
- Urinary tract infection
- Peripheral edema
- Upper abdominal pain, flatulence, diarrhea
- Influenza, pneumonia
- Acute cardiac failure
- Pain in extremity, myalgia
- Punctate keratitis
- Vaginal infection
- Laboratory abnormalities: altered neutrophil and lymphocyte count, increased liver function test and blood urea nitrogen, increased prothrombin time, reduced serum thyroxine levels

Contraindications:

- Hypersensitivity.
- During pregnancy or breastfeeding, and for women of childbearing potential not using contraception.
- Due to sorbitol in the capsules, it should not be given to patients with hereditary fructose intolerance.

Drug interactions:

- Avoid the combination of tafamidis with alpelisib, berotralstat, cladribine, ubrogepant, pazopanib, rimegepant, or topotecan.
- Dose adjustment may be required when used with substrates of breast cancer resistant protein (BCRP) transporter (e.g., methotrexate, rosuvastatin, imatinib).

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